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DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF THE INITIAL GENETIC ABNORMALITIES IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
(Experience of Hungarian Pediatric Oncology Study Group,1993-96)*

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The initial genetic changes (chromosome abnormalities, DNA ploidy) in ALL proved to be one of the most reliable prognostic parameters leading to the suggestion of developing genotype-specific therapy. While the prognosis in patients with pseudodiploid karyotype is usually unfavorable, a significantly better prognosis can be observed in those with more than 50 chromosomes. Therefore, the reliable and accurate identification of patients with >50 chromosomes is of particular importance. A nationwide project has been established in Hungary is order to perform the initial genetic analysis of all children diagnosed in the ten hematological/oncological centers of the country using cytogenetic methods, DNA flow cytometry and FISH technique. The data obtained on 187 ALL patients diagnosed in 1993-95 and those diagnosed in 1996 are presented and the results are compared to those in the literature. Based on the results of 75% of the patients investigated cytogenetically successfully related to the data of flow cytometry and FISH a difference between our data and those in the literature was found: a/ a lower ratio of hyperdiploid cases was observed; b/ thepattern of chromosome involvement proved to be different: in addition to trisomies of chromosomes 4, 6, 10, 14, 17, 18, 21 and X which are known to be most frequently involved chromosomes, trisomies of chromosomes 3, 8, 11 and 13 were also observed with a high frequency; c/ although the duration of follow up is rather short, no favorable prognosis of hyperdiploid patients could be proved in our material. These differences may reflect real geographic characteristics and may be related to different environmental mutagen/carcinogen effects of the given geographic area. In order to determine whether or not these differences really exist further genetic studies on ALL patients in Hungary seems to be essential.

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TREATMENT INTENSIFICATION WITH BFM-LIKE BLOCK THERAPY DID NOT IMPROVE CONTROL OF HIGH-RISK LEUKEMIA RELAPSE. PRELIMINARY RESULTS OF AIEOP ALL 91 STUDY.

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Background - In the attempt to improve the cure rate of high-risk acute lymphoblastic leukemia (HR-ALL) in the HR arm of the AIEOP ALL 91 study, chemotherapy was intensified compared to previous study AIEOP ALL 88, and was based on the block-therapy used in the BFM ALL 90 study, and derived from the BFM REZ study for relapsed ALL.
Patients and methods: between march 1991 and april 1995, 187 pts (16% of the total) were defined as HR according to: high tumor burden (i.e. BFM risk index >1.7; n=60), or CNS leukemia (n=35), or t(9;22) (n=15), t(4;11) (n=3), prednisone poor response (n=52), no CR at day 33 (n=22). Chemotherapy consisted of the usual Ia induction therapy, followed by cranial radiotherapy and nine blocks containing non-cross resistant drugs, administered q 21 days; continuation therapy was based on oral 6-MP and i.m. MTX. Median follow-up time is 29 months.
Results – Of the 187 patients, 29 (15%) failed to achieve CR (11 deaths, 18 resistant), 53 relapsed (28%) in the marrow (n=49, including 8 combined) or isolated in the CNS (n=2), or other (n=2); 7 patients (3.7%) died in CR. The pEFS (SE) at 4 years is 39.5% (4.7). These results did not improve those obtained in HR arm of the previous study 88 with conventional BFM chemotherapy, for the subgroup of patients identified with the same criteria (n= 111, 8 induction failures, 38 relapses).
Discussion - Despite massive therapeutic effort, including a significant toxicity and prolonged hospitalization, excessive marrow relapse during and after treatment completion was responsible for unsatisfactory result. In particular treatment intensification with block therapy was not effective in improving control of HR-ALL. Intermittent therapy and lack of protocol II might be responsible for this failure.

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HD IN CHILDREN: TREATMENT RESULTS.

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Devising new strategies for the treatment of children with HD is problematic due to the overall success of current treatment regimens. Also it is complicated by increased risk for adverse effects of chemotherapy (CT) and radiotherapy (RT). The aim of the study was to compare the effectiveness of different schedules of combined treatment.
Patients and Methods: 570 pts with HD were treated according to four treatment schedules (I - IV groups). The differences between groups were: 1) refusal of diagnostic laparotomy and spleenectomy, 2) definition of risk factors and grouping pts into different risk categories, 3) determination of the optimal chemotherapy agents (MOPP, DOPP, COPP), 4) inclusion of antracyclins into schedules of treatment, 5)minimization of volume and total dose of RT and overall duration of combined treatment, 6)including immunomodulatiors.
Results: In 193 pts of group I 5-year relapse-free survival (RFS) was 81,3%. Relapse after initial therapy was in 12,4% pts and second primaries - in 1,7%. In 143 pts of group II RFS was 93,8%, relapse rate - 11,9% and second primaries - 1,4%. In 117 pts of group III RFS was 92,4%, relapse rate - 12,3%. The median follow-up in IV group pts was 28 month. The complete response was 98% and relapse rate - 6,7%.
Conclusion: The use of combined therapy provided excellent disease control with the potential for diminished toxicity from I to IV schedules. The most effective schedule was combined modality (CT+RT) treatment considering risk factors.

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B-CELL NON-HODGKIN'S LYMPHOMA IN CHILDREN.

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The objective of the study: Improvement of the treatment results in children with B-cell NHL.
The methods: For the period of 1993 - 1996 there were 43 children with NHL evaluated and treated in The Children's Cancer Research Institute. Out of them 29 patients had B-cell NHL. The age of the children varied from 1 up to 14 years. Male/female ratio - 2:1. The locations of the tumor were: abdominal cavity - in 12, Waldeyer ring - in 7, jaw - in 4 patients. 6 other children were diagnosed to have orbit, testis, mediastinum, bone and lymphatic node primary involvement. One child had generalized disease at admission with unknown primary site. All

patients had comprehensive evaluation including biopsy prior therapy. The children were staged according Murphy's staging system: Stage I - 1, stage II - 10, stage III - 11 and stage IV - 7 patients. The treatment was carried out according to modified BFM-90 clinical protocol with maximum systemic methotrexate single dose 1000 mg/m.sq.

Results: The complete remission was obtained in 26 patients and partial effect with further tumor progression - in 3 cases. 3 children died because of treatment complications during effective induction therapy. One patient developed bone-marrow relapse in 12 months after completion of therapy. Retreatment with BFM-90 high-risk All protocol allowed to achieve second complete remission lasting 18 months. 23 patients in first remission survive 12-46 months from the start of therapy. Side-effects and complications included cytopenia, sepsis, mucositis and enteropathy.

Conclusion: Modified BFM-90 protocol is an effective but rather toxic treatment of B-cell childhood NHL. Accumulation of experience may allow to reduce the number and severity of side-effects and complications and to improve the final results of treatment.

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PREDICTION OF EARLY DEATH IN CHILDREN AND ADOLESCENTS WITH HODGKIN'S DISEASE

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Background: Long term survival in patients with Hodgkin's disease (HD) is about 75 % using different therapeutic regimens. An unsolved question is identification of pts at high risk for treatment failure. The aim of our study was to identify factors which could predict early deaths in 159 young pts treated at our institute for HD in the period of 1970-1994.

Patients and methods: There were 94 boys and 65 girls, 2-18 (mean 12) years old. The usual staging procedures were performed including lymphangiography and laparatomy (61 pts). Stage I-II had 65 %, stage III-IV 35 %, B symptoms 23 %, bulky disease 40 % (half of them mediastinal) and extension to parenchymal organs 9 % of the pts. The histology was LP 4 %, NS 56 %, MC 35 % and 5 % unclassified. Radiotherapy (RT) was the first treatment in 29 %, chemotherapy (Cht) in 8 % and a combination of both in 63 % of the pts. The follow up time (December 31 1996) was 2-26 years.

Results: Of the 159 pts 25 are dead, 14 (9 %) died during the first 2 years (2-20 months) from diagnosis. The cause of death was virus infection in 4, DIC in 1, ARDS in 1 and HD in 8 pts. Five of the latter (all but one had bulky mediastinum) were resistent to primary treatment (Cht 2, Cht and RT 3). Three pts had early relaps after RT (1) or combined treatment (2). Significant for prediction of early deaths by univariate factor analysis were: advanced stage, bulky mediastinal disease, lung hilus involvement, extension to parenchymal organs and refractory disease to primary treatment.

Conclusion: To diminish the risk for early death in the high risk group it is necessary to intensify treatment and to prevent virus infection.

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PARTICULARITIES OF IMMUNOPHENOTYPING OF ALL IN THE WESTERN PART OF ROMANIA

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The Pediatric Oncology Group has published statistical data about the subtypes of ALL which have been show that T-ALL represented 14%and B-ALL 85.6%,pre-B-ALL 18%; pre pre B-ALL 67% and pro B-ALL 0.4%. Our study was performed on 36 cases with ALL,admitted in the 3rd Paediatric Clinic Timisoara between 1992 to 1996.Immunophenotypic analyses were done by flowcytometrie(FACS-can)using monoclonal antibodies for Band T-cell.We found the following distribution of the ALL subtypes:pro B-ALL in 4 cases(11.11%),c-ALL(pre pre B-ALL)in 10 cases(27.77%),B-ALL in 2 cases (5.55%),T-ALL in 14 cases (38.88%)and unclassified ALL in 6 cases (16.66%).These data shows an increased number of the T-ALL comparatively with the percentage found in the Western Europe and USA,but a lower percentage comparatively to those found in some countries from the Eastern part of the world(T-ALL was found in India in 43.1% of the ALL and Egypt in 53% of the total ALL in children). It is to discuss the cause of these differences among the leukaemic lymphoblastic immunophenotypes: geographical,ethnical,ecological or socio-economical. The data can reveal a correlation with the socio-economical level of the respective geographical area.

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PRELIMINARY RESULTS OF THE TREATMENT OF CHILDREN WITH ALL ACCORDING TO THE BFM-ALL 90 M PROTOCOL IN RUSSIA AND KAZAKHSTAN

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Since 1991 year were organized 13 oncohematological centers in Russia and Kazakhstan by the support of the humanitarian society "CARE Deutschland".They are: I categorie: Khabarovsk, Novosibirsk, Ekaterinburg, Alma-Ata; II categorie: Voronezsh, Volgograd, Rostov, Chelyabinsk, Vladivostok, Novokusnezk, Perm, Omsk, Karaganda.

It gives a possiblity to treat children, suffering with leukemia and solid tumors, according to the morden technologies. 7 millions children live in the Centers' region. 492 little patients were treated in these centers according to the BFM -90 ALL (Minsk) Protocol - the modification of the German study with the MTX reduction to 1 g/m^2 during 36hr., brain irradiation (18 GY).

According to our data the rate of CR is obtained from 84% to 93%, non-responded and early death are noted in 7 - 16% of cases. The total 5-years EFS is 0,6 (Kaplan-Mayer estimates), but it is variable from center to center (0,4 - 0,8). 30% of patients develop or reactivate hepatitis (HV_B,HV_C,CMV) during the treatment which are not prevented because of the deficiency of medical supplies, laboratory modern test systems, medical and social conditions..

Conclusions: The BFM-90 ALL M Protocol was confirmed to be the basic and well studied in Russia and Kasakstan. It produces the rate of EFS about 0,6. Actual problems and the ways of their sollutioun are discussed in the abstract.

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A CASE OF CD 30-POSITIVE LARGE CELL ANAPLASTIC NON-HODGKIN-LYMPHOMA (Ki-1-LYMPHOMA OF 0-TYPE) ASSOCIATED WITH LEUKEMIC T-CELLS AND SKIN LESIONS

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We are presenting an uncommon case of large cell anaplastic lymphoma, Ki-1 of 0-type in a 17 y. o. male from Tchernobyl region (Pinsk, Belarus).

Patient A.L. was admitted to oncohematologycal center at Minsk because of complaints to weakness, weight loss and febrile episodes during last three weeks. Patient A.L. is a single child in the family. His parents and other relatives are healthy and without any genetic or oncological disordes. Our patient was healthy and studied in the college before disease. Since the time of admission the patient's condition deteriorated and a lymphadenopathy combined with respiratory failure appeared. Lymph node size were: neck 30-36 mm, axillary 26 - 28 mm, abdominal 20-40 mm in diameter.Papules and skin rash appeared on the face, trunk and arms. Chest X-ray examination showed mediastinum mass, pericarditis and pleuritis on both sides. The leukocyte counts were $164*10^3$/mcl with 63% of atypic small or medium sized mononuclear cells with unusual cleaved nuclei and medium rim of pale blue cytoplasm. Bone marrow was not involved.The biopsied cervical lymph node specimen showed a diffuse infiltration with medium-sized blasts of irregular nuclear form and pale basophilic abundant cytoplasm. The proliferative activity of the blasts was 50%, the lymph node cells were found to express CD30,but not CD45,CD20 and CD3.In pleural fluid some atypical blasts of similar morphology with expression of CD13 in over 80% were detectableThe diagnosis of large cell anaplastic lymphoma (Ki-1 lymphoma of 0-type) was made. High titers of EBV-Ig M were detectable. Biochemical analysis showed: LDH 765 U/l, CRP 6,25 mg/dl, Uric acid 13,8 mg/dl, Creatinine 0,7 mg/dl.Patient has been treated according to the protocol B-NHL-BFM 90M. We have finished only prophase with CP and Prednisone. During the treatment leukocyte count increased to $246*10^3$/mcl. Unfortunatly, the patient died during chemotherapy due to progression of main disease, respiratory and renal failure.

Conclusion: In our report, we would like to discuss the dynamic of disease and differential diagnosis with lymphomatoid papulosis and mycosis fungoides associated with Sezary's syndrome. In addition, reference will be made to the role of the Tchernobyl accident in the clinical course of Ki-1-lymphoma.

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LMB 89 AND LMT 89 PROTOCOLS FOR THE TREATMENT OF NON-HODGKIN LYMPHOMA IN CHILDREN: RESULTS OF A SINGLE INSTITUTION.

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Published data by French SFOP Group of protocols LMB and LMT 89 for the treatment of non-Hodgkin lymphomas in children showed a significant improvement in outcome both for patients with localized as for patients in stage IV, although other groups have identified a considerable toxicity with poorer results.

From January 1992 until January 1997, 31 patients were treated with those protocols at our Unit.

Twenty three of them had undifferentiated lymphomas (5 Group A, 14 Group B, and 4 Group C) and received risk-adapted chemotherapy according LMB-89. Three of them suffered early relapses (all in CNS) and died of the disease. One patient in group B showed also a CNS relapse but was rescued with alternative treatment. Actuarial survival at 57 months is 0.85 and event-free survival (EFS) is 0.81.

The 8 patients with lymphoblastic and large-cell lymphomas (1 in Murphy's stage II, 4 stage III, and 3 stage IV + CNS) were treated with LMT-89 protocol. One patient with stage IV + CNS had an early CNS relapse during consolidation and was subsequently rescued. Actuarial survival and EFS at 52 months is 0.85.

No toxic deaths were observed but toxicity was severe during the induction courses with myelodeppression and mucositis as the main toxicities, succesfully treated with hematopoyetic growth factors. Consolidation and manteinance courses were well tolerated. One patient was diagnosed of a second neoplasia (myeloblastic leukemia) 6 months after the completion of therapy and died subsequently. No other long- term adverse effects were observed.

Our results are in concordance with those of other groups aplying these protocols although the unusually high rates of early CNS relapses is worrysome.

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CLINICAL FEATURES AND TREATMENT OF MALIGNANT LYMPHOMAS IN CHILDREN OF KYRGYZSTAN

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There were 125 patients,including 54 with Hodgkin's disease and 71 with non-Hodgkin lymphoma.Treated at the Dept.of Pediatric Oncology [Bishkek,Kyrgystan] from 1986 through 1996.The severe course of Hodgkin's disease was observed in patients with the unfavorable prognostik factors.The inductive therapy included antibiotic-adriablastin during the first 3-6 courses of chemotherapy.The radiation therapy was reduced to 25 Gy on the local nodes.All the non-Hodgkin lymphoma patients had Stage III-IV of the disease. The treatment was performed in accordance with T- or B -type using BFM-protocol.The results of the treatment showed that complete clinical and hematologic remission [CR] was achieved in 95% of Hodgkin's desease cfses.The efficacy oft chemotherapy in non-Hodgkin lymphome patients varied in groups with different chemotherapy regimens: CR was observed in 80%,whereas in those with less intensive treatment CR was achieved only in 30% [17 out of 51].Thus,the treatment of malignant lymphomas with unfavorable prognostic factors should be intensive with administration of high doses of cytostatics in the beginning of the course for better eradication of pathologic clones.

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HODGKIN'S DISEASE IN CHILDREN; CLINICAL STAGING AND 5 YEARS RESULTS OF TREATMENT BY MODIFIED PROTOCOL DAL HD-90

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34 children with proved Hodgkin's disease were retrospectively evaluated according to clinical and pathological staging at initial diagnosis from 1988 to 1996 at the Paediatric Onco-haematologic Department. The patients were 2-16 years of age, 19 girls and 15 boys. 4 (11,8 %) patients had stage I, 16 (47 %) - stage II, 9 (26,5 %) stage III and 5 (14,7 %) had stage IV disease. Staging laparotomies were performed on 3 (8,8%) patients . 8 patients (23,6%) had histological findings of nodular sclerosis, 23(67,6%) had mixed cellularity and 3 (8,8 %) had lymphocyte predominance. Before 1992 it was no systemic treatment of Hodgkin's disease. After 1992, all patients were given therapy according to modified protocol DAL HD-90. 16 patients were followed up: 2 patients with stage I, 7 - stage II, 5 children with stage III and 2 - stage IV. Followed up period was 1- 5 years (mean of 3.5 years). Overall survival rate is 100%. We had no death on therapy as before. So, this program of treatment has high efficacy and moderate toxicity.

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MRI IN THE EVALUATION AND FOLLOW-UP OF EWİNG'S SARCOMA

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Objective: To detect effects of chemotherapy and radiotherapy in Ewing's sarcomas with MR imaging.
Methods: 15 patients (11 males, 4 females, age 6yrs to 16) with pretreatment MRI and at least 1 follow-up MRI (0.5-1.5 T) were evaluated retrospectively (average 4 MRI in the follow-up). Lesion size, signal intensity relative to muscles (in T1W, T2W and STIR images), enhancement patterns were evaluated and special attention was given to subperiosteal T2 hyperintense foci that enhance with Gd-DTPA. All the patients received chemotherapy according to the EICESS 92 protocol [cyclophosphamide, ifosfamide, actinomycin D and adriamycin (VAIA) or by high risk protocol with additional etoposide (EVAI)] and radiotherapy (4500-5500 cGy). Two patients had surgical resection.
Summary: 8 pts were in remission, 2 pts died and 5 pts are still receiving therapy. All the tumors had soft tissue component except one. Both the soft tissue and marrow component had high signal intensity in T2W and STIR images. IV contrast medium was very useful showing tumoral enhancement and revealing necrosis.
Regression of soft tissue mass was the earliest sign of effective therapy.
Subperiosteal hyperintense foci that enhanced with Gd-DTPA was present even in pts in remission. Fatty marrow conversion was a good prognostic sign when present.
Conclusion: MRI was very useful in demonstrating marrow and soft tissue infiltration in Ewing's sarcomas. Regression, necrosis and lowering of signal intensity were good response signs. Subperiosteal foci that persisted even in remission pts need to be evaluated with larger series to detect early relapse site.

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EVALUATION OF CHEMOTHERAPY NEPHROTOXICITY WITH Tc-99m DMSA AND Tc-99m EC SINTIGRAPHY IN RELATION TO CLINICAL AND BIOCHEMICAL PARAMETERS

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Objectives: This study investigated the relationship between toxic effects of ifosfamide and cisplatin assessed by clinical and biochemical parameters in relation to Tc-99m dimercaptosuccinic acid (DMSA) and Tc-99m N' -ethylen-l-dicysteine (EC) renal scintigraphy.
Patients and Method: Fourteen pediatric patients (6 boys and 9 girls) (2-16 yr) were investigated. Each received cisplatin (range 450-1100 mg/m^2) (mean ± S.D. 601 ± 164) and/or ifosfamide (range 9-54gr/ m^2) (mean ± S.D. 36±19) for various malignencies. Serial measurements of renal Tc-99m DMSA uptake were calculated and kidney function were assessed with Tc-99m EC scintigraphy before and after chemotheraphy.
Results: All except 2 patients had normal levels of DMSA uptake (17%-29%, mean ± S.D. 21% ± 4) at baseline study. Two patients had reduced uptake unilaterally which was due to tumor invasion. Following chemotherapy, DMSA uptake showed severe reduction in 5 with or without clinical nephrotoxicity. The most common observed pattern was homegenously decreased uptake and elevated background activity. Two patients with decreased DMSA uptake were found to have normal tubular function according to biochemical investigations which suggested subclinical injury. The overall degree of nephrotoxicity, however was not apperent on Tc-99m EC scintigraphy in most of the cases and 3 patients with overt renal dysfunction due to tumor compression, involvement or surgical complication displayed decreased perfusion, concentration and excretion of the radiopharmoceutical.
Conclusion: In this study, we found that ifosfamide induced renal tubular damage can be asssessed with Tc-99m DMSA scintigraphy before chemotheraphy associated nephrotoxicty is detected by laboratory measurements. The results also imply Tc- 99m EC scintigraphy is not able to detect subclinical injury or predict high risk during treatment. The final role of Tc-99m DMSA scintigraphy in detection of renal tubuar dysfunction due to chemotheraphy is yet to be determined is still under investigation.

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CHANGES IN BONE MINERAL DENSITY OF CHILDREN WITH CANCER DURING ONE-YEAR-FOLLOW-UP

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The bone mineral density (BMD), which is correlated with age and weight, peaks at puberty, especially at the second stage, then does not show significant changes. The objective of this study was to determine the side effects of chemotherapy (CT) including steroids and/or RT schedules on bone mass in children with different malignities in a longitudinal study.
The BMD (g/cm^2) of lumbar vertebral bone (L2,L3,L4) from anterioposterior and lateral views was measured four times a year (at the beginning of diagnosis, 3, 6 and 12 months later after therapy instituted) by Dual Energy X-Ray Absorptiometry (DEXA) in 17 children with cancer aged 2-17 years. To eliminate the effects of puberty on BMD, 7 adolescents with cancer in advanced stages of puberty (aged 14-17 years) were compared to 9 healthy adolescents (aged 13-16 years) at the same stage of puberty.
Results: The mean BMD value of L2 vertebrate was 0.631±0.207 g/cm^2 at the beginning, 0.677±0.234 at 3rd month, 0.585±0.174 at 6th month and 0.624±0.160 g/cm^2 at 12th month, respectively. Children and adolescents receiving CT and/or RT schedule didn't show any significant changes in BMD when the values obtained at 0, 3rd, 6th and 12th months were compared to each other (p>0.05). Patients receiving steroids in leukemia and NHL protocols had also no marked changes in BMD examinations as same as the other patients with solid tumors (p>0.05).
The BMD was found to be correlated with age at the beginning (r=0.853, p<0.001) and one year later (r=0.698, p<0.01). Seven adolescents didn't develop any significant changes in BMD during one-year of follow-up as expected (p>0.05).
Conclusion: Children and adolescents with cancer, including those treated with CT and/or RT, don't appear to have adversely affected bone mass during one-year-follow-up.

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VALUE OF NUCLEAR MAGNETIC RESONANCE (NMR) IMAGING IN DIAGNOSIS AND MONITORISATION OF METHOTREXATE (MTX) INDUCED LEUCOANCEPHALOPATHY

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Patients with malignancies taking MTX (IV or IT) for central nervous system prophylaxies are under risk for leucoancephalopathy. In these patients detection of neurologic abnormalities before the apparence of clinicopathologic findings is needed. The aim of this study is to evaluate the feasibility of NMR in early diagnosis and monitorisation of MTX induced leucoancephalopathy.

Materials and methods ; 27 patients with pediatric malignancies (21 ALL, 4 NHL, 2 Osteosarkom) ages between 1,5-14 years were included in this study. All were given IV (moderete or high) and IT MTX. Patients who had taken radiotherapy were excluded. Serial NMR studies were performed at the beginning, during induction and at the end of the treatment..

Results; NMR findings of chronic leucoancephalopaty (HIA;High intensity areas) were evident in 7 cases (25,9%) and clinical neuropathology was found in two of them (7.4 %). Leucoancephalopaty resolved in one case , while in the other six cases, NMR findings continued without progression. Mean cumulative IV MTX dose was 2526 mg in patients with HIA (+) NMR findings and 7346 mg in patients with HIA (-) NMR findings (p>0,05) mean IT cumulative dose of methotrexate was 77,14 mg and 99,6 mg in HIA(+) NMR and HIA(-)NMR findings respectively (p< 0,05).

Conclusion; Even thought the treatment with MTX (IV,IT) was not interrupted, MTX neurotoxicity showed no progression. No correlation was found between cumulative IV MTX doses and the development of leucoancephalopaty. Cumulative dose of IT MTX was significantly lower in patients with HIA (+) NMR, supporting the role of hypersensitivity in development of leucoencephalopaty. These data suggest that NMR is a very a sensitive technique for monitoring CNS abnormalities in children treated with MTX.

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EPIDEMIOLOGY OF ACUTE LEUKAEMIA IN CHILDREN IN THE ECOLOGICALLY UNFAVOURABLE REGION OF SIBERIA

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This paper presents the results of the 38-years study of frequency and distribution of ac-

ute leukaemia in children in Tomsk region.Three last years (1993,1994,1995) are analysed separately because of the deterioration of the ecological situation after the accident at Siberian Chemical plant (SCP).

The analysis has shown that the primary occurence of acute leukaemia in children over the 35-years period (1958-1992) is 3.29 per 100000 children population. This index is average and close to those recorded in the literature. Variations of the occurence of the disease with the rise in definite years have been observed. Straightening of the curve by the method of the smallest squares shows a stable slow rise of the disease occurence during these years. Spatial-temporal ratio of the disease occurence has not been found, however the cyclic elevations within the intervals of 2-4 years have been observed.

The dynamics of the occurence of acute leukaemia in children due to the deterioration of the ecological situation after the accident at SCP is of particular interest. The study has shown that the disease rate in 1993,1995 remained within the average. In 1994 the growth of this index was noted. It is likely to be a new cyclic growth.

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Anthropometric indicators and prognosis in Wilms' tumor

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To evaluate if nutritional status is a prognostic factor for survival in Wilms' tumor we analyzed three common anthropometric indicators as defined by the National Center for Health Statistics: weight-for-age (WA), height-for-age (HA), and weight-for-height (WH) in 518 children with Wilms' tumor enrolled in successive clinical trials by the Brazilian Wilms' Tumor Study Group during the period October 1986 to February 1994. The cutoff points yielding significant prognostic effects for death and relapse rates were the 40th percentile (40p) for WA and the 70th percentile (70p) for HA. The WH indicator was not significantly associated with risk of death or of relapse. Potential confounders included in multivariate analyses were hospital, race, age, protocol violation, stage, protocol and the remaining anthropometric indicators. The hazard ratio (HR) for overall survival for patients with WA above the 40p vs. those below was 0.60 (95% confidence interval [95%CI]: 0.40-89). After adjusting for confounders the HR was 0.75 (95%CI: 0.48-1.18). The HRs for relapse-free survival were 0.78 (crude, 95%CI: 0.57-1.08) and 0.99 (95%CI: 0.69-1.42) after adjustment. The HR for overall survival for patients with HA above the 70p was 0.46 (crude, 95%CI: 0.28-0.77) and 0.69 (95%CI: 0.39-1.22) after adjustment. The HR for relapse-free survival contrasting those with HA above 70th vs. those below was 0.51 (crude, 95%CI: 0.34-0.78) and 0.65 (95%CI: 0.41-1.03) after adjustment. HA above the 70p was a predictor of lung relapse before adjustment for confounders (HR=0.49, 95%CI: 0.26-0.95), the effect disappearing after controlling for the above covariates (HR=0.62, 95%CI: 0.30-1.28).

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EPIDEMIOLOGICAL SURVEY AND TREATMENT OUTCOME IN CHILDHOOD NON-HODGKIN LYMPHOMA (NHL) 1993-1996 IN THE NORDIC COUNTRIES.

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The Nordic NHL Study Group (NOPHO-NHL) has since the last epidemiologic report in 1992 established the use of a common protocol for work-up, treatment and follow up. The material is population based without loss of patients at the follow up Jan 1, 1997. Staging is by Murphy with the BFM-modification for B-NHL and LCAL-NHL. Patients with B-and LCAL-NHL were treated with short, intensive protocols (BFM) while pre-B and T-NHL were treated with modified NOPHO-ALL protocols. During the four year period Jan 1, 1993 to Dec 31, 1996 NHL was diagnosed in 157 children below 15 years of age at diagnosis. The annual incidence was 0.9 per 100.000 children with a male/female ratio of 3:1 and the median age at diagnosis was 9 years. 92% of the children had caucasian background. Data on immunophenotype was possible to evaluate in all but four patients: 9% had pre-B, 24% T, 52% B, 12% LCAL-NHL and 3% were unclassified. Of the 157 children 17% had stage I, 21% stage II, 46% Stage III and 16 % stage IV disease. The p-EFS for the whole group was 0.81+/-0.04 at four years. p-EFS for B-NHL and non-B (pre-B and T)-NHL was equal and 0.87+/-0.06, while for LCAL-NHL 0.67+/-0.12 and of the unclassified patients only one out of four was in remission at follow up. Twenty children have so far had an event, eight of them belonged to the unclassified or LCAL-NHL groups. Treatment results are in parity with those of other international groups'. The increase in incidence since our last report was to be expected with the establishment of a new common nordic protocol.

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INFANT LEUKEMIA IN THE NORDIC COUNTRIES THE NOPHO EXPERIENCE 1985 - 1995.

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168 children below 18 months were diagnosed with acute leukemia. 99 ALL and 69 AML.
ALL : 23 were < 6 months and 52 were < 1 year at diagnosis comprising 2,5 % of all ALL cases < 15.
AML: 18 were <6 months, and 41 were < 1 year corresponding to 13% of the AML cases.
Children 12-<18 months (47 ALL, 28 AML) were included for comparison.
The total population is 22,5 million with 4,5 million children <15 years. Each year there will be 8-10 new cases of acute leukemias in infants < 1year, half of them ALL.
AML treatment was according to NOPHO protocols but ALL treatment for the infants was individual, usually according to intermediate risk protocols, BFM type, with very varied dose reduction/ adaptation policy.
The EFS for ALL < 6 months, 6-<12 months and 12-<18 months were 0,13, 0,41 and 0,76 respectively (p<0,01). 7/23 infants below 6 months never attained remission. Age was of significance for ALL but not for AML patients. Corresponding p-EFS values for AML were 0,49, 0,50 and 0,38 respectively.
65% of infants < 6months with ALL had a WBC ≥ 100. For all infants < 1 year the p-EFS was 0,12 for WBC ≥ 100 compared to 0,39 for WBC < 100 (p<0,01). Of the 15 children below 6 months with cytogenetic analysis available 4 had t(4:11), one t(11:19) and one 11q-deletion.
Next protocol needs to: improve diagnosis of MLL rearrangement, intensify treatment related to the risk factors and specify any necessary dose adaptation.

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INTRACRANIAL PRIMITIVE NEUROECTODERMAL TUMORS IN CHILDHOOD: REVIEW OF 105 CASES IN A SINGLE CENTRE

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Objective: Identification of parameters of prognostic value by analysing the medical data of a large series of intracranial (IC) PNETs in children, treated according to different protocols.
Methods: Retrospective analysis of the medical data of all children with IC PNET that were referred to the Emma Kinderziekenhuis/Academic Medical Center in Amsterdam, from 1968 till 1994. Patients were followed till januari 1996. Survival and eventfree survival were calculated and univariate analysis was performed to detect important prognostic factors.
Results: In total, 105 children were treated for intracranial PNET (ratio boys: girls was 2:1) according to different protocols. One hundred and one patients were operated upon, from which 89 received radiotherapy. Of these 89, 61 received adjuvant chemotherapy. The mean age at the time of diagnosis was 7.0 years. The 5-year EFS and overall survival were 55 and 58 % respectively.
Conclusion: The presence of leptomeningeal metastases and/or tumorcells in the cerebrospinal fluid had a significant influence on prognosis, as did the extend of surgical resection and the radiation dosage on the posterior fossa. Patients who needed a ventriculoperitoneal or -cardial shunt for a long time during their treatment had a significantly worse prognosis than those who did not or only temporarily need a shunt. There was no statistical significant influence of the interval between the operation and the start of radiotherapy or the addition of chemotherapy. However, one chemotherapyprotocol (prednison, methotrexate and vincristin immediately after the operation) seemed to give a better result than others.

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VARICELLA ZOSTER INFECTIONS IN NEUROBLASTOMA (NB) CHILDREN. ANALYSIS OF ONE INSTITUTION.

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Introduction
Clinical observations of chickenpox (cp) in NB children, usually showed the progression of the disease in the advanced stages of NB, during or after the cp. To confirm the hypothesis, all cases of cp in NB cases,treated between 1966 and 1996,were reviewed.
Material
From 1966 to 1996, 47 NB children with cp were observed. The stages of advancement of the investigated population were:I-1,II-0,IVS-2,III-10, III/IV-8(children who were initially in stage III, but developed metastases during the course of treatment),IV-26. At the same time 280 NB children, including those with cp, were treated:stage I-9, II-30, IVS-20, III-46, III/IV-33,IV-142.
Results
The 1 stage I survivor (1/9 children), did not develop progression after the viral infection. The same was in stage IVS survivors (2/20-10%). In stage III (10/46 -21.7%) the progression after the cp was not noted in 9 children. All are alive. In stage III/IV (8/33-24.2%) all children developed progression after the cp. In 2 children first cp did not result in progression, but the second led to spread of the disease. All 8 stage III/IV died. All, but 3 stage IV children (26/142-18%) developed progression after cp and finaly died. 3 stage IV survivors were 10,12, and 16mos of age.
Conclusions
Genetic explenation of the influence of herpes virus infection on the progression during the course of neuroblastoma should be investigated.

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SPECIFIC CUTANEOUS INFILTRATES IN CHILDREN WITH LYMPHOBLASTIC LYMPHOMA.

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Scant information is available concerning the occurrence and natural history of specific skin involvement in children with lymphoblastic lymphoma (LBL). One hundred and five children with LBL were enrolled in the multicenter trial EORTC 58881 of the Children's Leukemia Cooperative Group. LBL with mature B-cell immunophenotype were excluded from this trial. Eleven children presented with specific skin involvement at diagnosis. This group consisted of 4 boys and 7 girls (median age, 5 years; range, 4 months - 11 years). There were 1 stage I, 3 stage II, 1 stage III and 6 stage IV lymphomas according to the Murphy classification. Among the 9 cases evaluable for immunophenotype, one case belonged to the T-lineage and 8 belonged to the B-lineage (positivity for CD 19): common (CD10+) 5 cases (however Cμ expression was not determined in 2 cases) and pre B (Cμ+) 3 cases. Skin lesions were observed within a median time of 2 months (range, 6 weeks - 5 months) before the diagnosis of the LBL. Among the 11 children, 9 had at least one skin lesion located on the head. Eight children had a single skin lesion and 3 children had 2 to 4 lesions. The lesions were asymptomatic indurated papules or nodules, brown-red to violaceous without excoriation or ulceration. The size of the lesions varied from 0.5 cm to 6.5 cm. Biopsies of the skin lesions were performed in 10 patients: in all specimens, the histologic examination revealed lymphoblastic cells infiltrating the dermis and the underlying tissue with uninvolved epidermis. Complete remission was obtained in all patients following induction chemotherapy. Eight children remained in first complete remission (median follow-up of 5 years: range, 14 months - 7 years) whilst 3 relapsed (2 are in second remission with a follow-up of 7 and 36 months).
The present study demonstrates that specific cutaneous involvement is not a rare event and can represent an early manifestation of LBL. Cutaneous involvement in children with LBL is correlated with a B-cell precursor immunophenotype of the lymphomatous cells. The most frequent location of specific skin lesions in children with LBL is on the head. In our study, the prognosis of children with such involvement does not appear to be different from that of other patients without initial cutaneous involvement.

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SECOND MALIGNANT NEOPLASMS (SMN) AMONG PATIENTS TREATED FOR RETINOBLASTOMA AT ST. JUDE CHILDREN'S RESEARCH HOSPITAL; THE FREQUENT AND THE UNUSUAL.

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Among 170 children, 85 boys and 85 girls, treated for retinoblastoma at our hospital since 1962, 75 had bilateral disease. Ages ranged from birth to 16.2 years (median = 1.37). Ten have developed SMN, eight following bilateral retinoblastoma: For these eight patients, the median time to occurence of SMN was 13.3 years, range 3.2-23 years; the diagnoses included five with osteosarcoma and one each with rhabdomyosarcoma, basal cell carcinoma, and Ewing sarcoma. Seven of eight were within the radiation volume. Two of five patients with osteosarcoma are living free of disease at 0.8 and 7 years from SMN. Other survivors include patients with basal cell carcinoma and rhabdomyosarcoma. The two SMN following unilateral retinoblastoma included papillary thyroid carcinoma (14 years after enucleation), and meningioma (fifteen years after enucleation and irradiation). The patient with meningioma died without treatment, due to tumor and metabolic abnormalities. Treatment, appropriate for SMN histology and extent, was given to eight children; the second exception was a patient with osteosarcoma whose parents refused. Cumulative incidence, % (CI_{95}), of SMN for patients with bilateral retinoblastoma was 3.4 at 10 years (0.0,8.23), 15.5 (4.2,26.7) at 20 years and 21.4(5.6,37.2) at 25 years from diagnosis. For patients with unilateral disease, the cumulative incidence of SMN was 3.7 (0,9.0) at 20 years. Surveillance is required throughout the lifetime of survivors of unilateral and bilateral retinoblastoma (Supported by USPHS Grants CA23099 and CA21765, and by ALSAC).

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RISK FACTORS FOR THE DEVELOPMENT OF SPORADIC RETINOBLASTOMA: A CASE-CONTROL STUDY IN MEXICO

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The objective is to describe gestational and pre-conceptional risk factors for the development of sporadic retinoblastoma in Central Mexico.
The method used is a retrospective case-control study design. A questionnaire was used to assess exposure to potential risk factors for development of retinoblastoma. The questionnaire focused on potential mutagenic exposures (environmental, occupational, and dietary) occurring prior to conception, and during gestation of the index child. It was administered as an interview to parents of children treated at the Instituto Nacional de Pediatría (INP) in Mexico City. Cases (n=107) included children (age < 6) with newly diagnosed non-familial retinoblastoma. Controls (n=196) were children (age < 6) referred non-emergently to the INP. Exclusion criteria included a diagnosis of another malignancy or genetic syndrome. Statistical analysis is currently underway using the Mantel Haenszel chi-square test for dichotomous exposure variables, and multiple logistic regression to control for potential multiple confounders.
Conclusions: Preliminary analyses suggest that there are differences in maternal dietary intake during gestation and in parental age at conception. Prior studies suggest that incidence of sporadic retinoblastoma may be related to risk factors associated with low socio-economic status. If increased risk were detected in the final analyses of our study, we expect to be able to better characterize these risk factors and propose mechanistic hypotheses that may explain their relevance to the molecular lesions associated with this disease.

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NON-HODGKIN LYMPHOMAS IN CHILDREN: EPIDEMIOLOGICAL FEATURES IN THE TIMIS COUNTY

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In the context of a general increase of neoplastic diseases during childhood in the Timis county in the last 18 years (from 5.03/100.000/year to 16.2/100.000/year) there can be observed a discordant high incidence of non-Hodgkin lymphomas (NHL): an average of 0.87/100.000/year in 1979-1988, 2.94/100.000/year in 1984-1988, and 4.7/100.000/year in 1989 up to now. In the meantime the incidence of leukemia, was maintained at a medium value of 3.9/100.000/year with the highest incidence of 5.5-6.5/100.000/year in 1985, and 1986 respectively. In the last period, in both entities, NHL and leukemia a great proportion of T cell proliferation was remarked. An environmental exploration for organochlorinated pesticides and environmental radioactivity, a biomonitoring of heavy metals in biophites (Cd, Cr, Cu, Ni, Pb, V, Zn) and a serological survey for Epstein-Barr virus (EB), HIV 1 and 2, HTLV I and II have been done. High pollution, especially with insecticides (hexaclorciclohexan and pDDE) was pointed out not only in the environmental medium, but also in the maternal milk. NHL was related to HIV 1 infection in 2, to HTLV I in 1, to HTLV II in 1, and to EB in 3 cases.

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IMPAIRED ANDROGEN PRODUCTION IN FEMALE ADOLESCENTS AND YOUNG ADULTS AFTER TOTAL BODY IRRADIATION PRIOR TO BMT

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Ovarian dysfunction, usually based on elevated gonadotropin and low estradiol levels, is a common finding after total body irradiation (TBI) containing transplant programs. Androgens, produced both by ovaries and adrenal cortex, are also important for the development of female secondary sexual characteristics and they may influence libido and the quality of sexual life which are often impaired in females after TBI.
Patients and methods: Pubertal development and androgen production were evaluated 1-10 years after BMT in 15 females aged 14-23 (mean 17) years. Before BMT, these patients had received combination chemotherapy for hematologic malignancy, and all had had a transplant program including TBI. At the time of the study, 3 patients were early to midpubertal and 12 late pubertal or postpubertal. Three patients were menstruating spontaneously. Twelve patients were receiving sex steroid substitution therapy. Serum concentrations of testosterone, androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate were determined. Androgen levels of late pubertal and postpubertal transplanted patients were compared with 19 post-menarcheal conventionally treated leukemia patients aged 14-21 (mean 17) years. Testosterone levels of 52 healthy postmenarcheal females aged 14-29 (mean 19) years were measured for control.
Results: The androgen levels of the BMT patients were lower than those of the conventionally treated patients. The differences in testosterone, androstenedione, and DHEA levels were significant. Three spontaneously menstruating BMT patients had normal androgen levels. The testosterone levels of the conventionally treated patients and the healthy controls were similar.
Conclusions: Subnormal androgen production might be one factor behind the problems in pubertal development and sexual life experienced by females after BMT. The usefulness of these hormone levels for follow-up purposes and the potential value of androgen replacement therapy in females after TBI merit further studies.

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MOTOR PROBLEMS OF CHILDREN DURING TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL).

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Introduction. In a late effects study, we have shown that about 60% of the children 2 years after treatment for ALL still have fine motor and/or handwriting problems probably due to late effects of Vincristine polyneuropathy. In the present study we have investigated motor functioning of children with ALL during treatment.

Patients. Motor functioning of 14 patients aged 4 to 12 years old (6 patients older than 7) at diagnosis was studied during treatment for ALL according to protocol DCLSG-ALL-8. In this protocol children receive 2 blocks of 4 gifts Vincristine (1,5 mg/m2/gift), one gift a week, the two blocks being 3-4 months apart. Informed consent of all patients was obtained.

Methods. The Movement Assessment Battery for Children (Movement ABC) was used to get overall information about motor functioning of the children. This test contains age related norms and consists of 3 subtests: manual skills, ball skills and balance. The summation of the scores on the subtests gives a total motor score.
The 'Concise Evaluation Scale for Children's Handwriting' (BHK) was used to study the quality and velocity of handwriting performance.

Results. Of the available scores, for manual skills 17%, for ball skills 20% and for balance 49% were ≤ 15th percentile, which means a borderline or

worse performance. Six patients performed the BHK; 3 wrote dysgraphic and 1 wrote too slow already before the first Vincristine gift was given.

Conclusion. In contrast with the late effects study revealing fine motor and/or handwriting problems, children *during* treatment for ALL showed balance problems in 49% of the tests while handwriting in this early follow-up period remained unchanged.

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Low Incidence of Cardiotoxicity Following Daunorubicin and Doxorubicin at A 10 Year Follow up.

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We used a battery of non invasive tests to evaluate the cardiac toxicity in 205 childdren and young adults who had received therapy for ALL and NHL.194 patients of ALL on MCP 841 protocol received 390 mg/m^2 of daunomycin over 2 yrs. and 11 patients of NHL on MCP-842 protocol received 160 mg/m^2 of adriamycin over 8 months. Each patient underwent at least 2 of the following tests 1) Electrocardiogram(ECG). 2) 2-D-Echocardiography. 3) Radionuclidde cardiac scan (MUGA-Technetium 99m multi gated acquisition). Clinically cardiotoxicity was not detected. The study was carried out 4 months to 10 yrs. after the patients finished the entire treatment. MUGA and ECG were done one yearly. The age of patients ranged between 1.5 to 46 yrs.(median of 8 yrs.). The MUGA was considered abnormal if global ejection fraction was below 45%. Only six patients had an abnormal MUGA where 2D Echo revealed mild LV dysfunction. All the patients were asymptomatic and are doing well. Three patients were detected within four months post therapy,two about a year later and the last one was detectedd two years post therapy. Wall motion abnormality was also studied and it was found that 3 patients had decreased the lateral wall motion. A patient with corrected Fallots tetralogy had right bundle branch block at the time of starting the treatment. There is no sign of cardiotoxicity 4 years post therapy. Another patient had corrected Transposition of great vessels,was operated at the age of 3 months and is doing well. Her pretherapy cardiac evaluation was normal. She has received 270 mg/m^2 of daunomycin. Thus we conclude that a cumulative dose of 390 mg/m^2 of daunomycin and 160 mg/m^2 of doxorubicin is safe.

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LONG-TERM SEQUELAE AFTER TREATMENT FOR A BRAIN TUMOR DURING CHILDHOOD

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Objectives: To investigate long-term problems in patients treated for a brain tumor during childhood.
Methods: The study-population existed of 51 survivors treated for a brain tumor under the age of 18, between 1974 and 1990 at the Free University Hospital in Amsterdam. The patients were evaluated more than 5 years after treatment using a written questionnaire about the physical, cognitive and social functioning. The responding group (n=32) was composed of 17 boys and 15 girls aged 7 to 30 years (median: 18,5). 16/32 had infra-tentorial, 9/32 hemispheral and 7/32 a midline tumor. The histological diagnoses varied widely. Treatment consisted of (sub)total tumor resections for most (31/32), followed by local radiotherapy (RT) in 9 and craniospinal RT in 4 cases, while chemotherapy was delivered in only 4 patients.
Results: Long-term effects on somatic functioning were as follows: motor impairment (11), epilepsy (7), problems in coordination (16), visual impairment (8), auditive impairment (7), endocrinological deficits (7) of which 5/7 had had a midline tumor. Cognitive functioning was impaired in concentration/ attention (15), memory (10), reading/writing (13) and speech (11). Concerning social functioning, 7/20 patients still attending school, received adapted education. 4/12 patients not attending school anymore, were not able to execute a regular job. No major differences were found between the group of irradiated and non irradiated patients.
Conclusions: Major deficits are observed in these survivors of childhood brain tumors in somatic (neurologic and endocrinologic), cognitive and social functioning. Follow-up is important to signalize complications at an early stage and give appropriate supportive care; and also to find a balance between the benefits and the risks of the treatment.

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INTRON A IN TREATMENT OF VIRAL CHRONIC HEPATITIS IN CHILDREN WITH ONCOHEMATOLOGICAL DISEASES.

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Viral hepatitis B,C appears to be a cause of chronical liver disease in 70% of patients with oncohematological diseases. The patients are revealed on base of hepato-spleen syndrom and/or hyperenzymemia presented.

We have observed 217 patients with oncogematological diseases with remission in terms from 1 to 7 years (9,3%-solid tumors and 90,6% hemoblastoses.2/3 patients were on chemotherapy, the rest were already out of treatment. HCV RNA and HBV DNA using the PCR method appeared to be positive in 48,4% of cases (HCV 31,3%, HBV - 9,7%, mixt infection C+B - 7,4%).Recombinant interferon-alfa-2b (Intron A) was used in 19 patients aged from 4 to 14 years (HCV-15, HBV -3, mixt-infection B+C - 1).An efficiecy was estimated in 15 children, have been receiving the therary more than 3 months. Absense of viral replication markers was noted in 11 patients in 3 and 6 months (73,3%); 4 children had the viremia (HCV -3, HCV+HBV - 1).Side effects were marked in 13 cases (fever above 38^0 - 13, trombocitopenia + leucopenia - 2, mialgia, skin rash in the places of injections and dryness of skin -1).

In such manner, a high efficiency Intron A in treatment of viral chronical hepatitis in children with oncogematological diseases was determined.

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NEUROLOGİC COMPLICATIONS OF CHILDHOOD MALINGNANCIES.

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Between Jan 1982 and Jun 1994, the records of 154 children with malignant non-CNS (Central Nervous System) tumors, excluding leukemias and lymphomas, were retrospectively reviewed. Fifty one (33.1%) cases had 69 neurological complications during the course of their disease. Thirty-eight (24.7%) cases had multiple neurologic complications. Nervous system metastasis was the most common neurologic complication (n=27;18.6%), which was followed by nervous system infection (n=17,11%). Spinal and cranial metastases were seen on 15 (9%) and,12 (7.7%) cases,respectively. Among the 12 cases with cranial metastases, 7 (4.5%) cases had brain metastases.The nerve plexus metastasis were seen on 3 (1.9%) cases. Twelve (9%) cases had treatment related peripheral or cranial neuropathies. Seven (4.5%) cases had new onset of grand-mall seizures. Each of the 3 cases had paraneoplastic syndrome, panhypopituitarism secondary to whole brain radiation, and iatrogenic Horner's syndrome, respectively. Three cases had developmental delay and mental retardation. These 51 patients with neurologic complications were followed for 9 to 102 months. Thirty (58.9%) patients were alive, 20 (35.2%) patients died and one case was lost, at the time of analysis. Among the 27 cases who had nervous system metastases, 19 of them died less than a year after diagnosis, and only 8 cases were alive at the end of the analysis. Neuroblastomas had the highest rate for causing the neurologic complication.
In conclusion; neurologic complications were seen on 33% of childhood solid malignancies and metastatic complications had dismal prognosis.

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QUALITY OF LIFE AFTER TREATMENT OF MALIGNANT LYMPHOMAS IN CHILDREN

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Objective: A group of 49 long-term survivors previously treated for non-Hodgkin lymphomas (20) and Hodgkin's disease (29) was followed up for late sequelae of the disease and its therapy and their influence on quality of life.
Methods: All of them were 2 or more years ($\bar{x}$ $6^{11}/_{12}$ y) without treatment in complete remission. The full clinical examination, endocrinological monitoring, high-resolution ECG (HC ECG) and pulmonary function tests were performed.
Summary: We observed: small abnormalities in function and/or structure of thyroid gland in 20 children; mild airway obstruction in 2 cases and restrictive ventilatory impairment in other two. 5 patients showed HC ECG abnormalities discovering discrete myocardial damage.
Only 4 of the long-term survivors had serious late complications influencing the quality of their life. [1] The secondary malabsorbtion syndrom after radical surgery for involvement of small intestine in one girl, who later suffered from primary hypotyreosis and diabetes mellitus type 1. [2] Serious kyphoscoliosis - after laminectomy and actinotherapy on the posterior mediastinum - with neurological symptoms and restrictive ventilatory impairment. [3] Growth retardation and hypergonadotropic hypogonadism. [4] Serious hypertension due to fibrotic changes of the previously infiltrated kidney.
Conclusions: We had observed undesirable effects in a half of the followed group but only in 8% the sequelae were serious enough to influence their quality of life.

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GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF) : VASCULITIS AND TUMORAL TRANSFORMATION RISK ASSESSED FROM THE FRENCH REGISTER OF SEVERE CHRONIC NEUTROPENIA (FR-SCN).

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Methods : Data collection on site (30 centers) was performed following the guidelines of the International SCN register. Diagnosis were reviewed by cytologist panel. The cut-off date for analysis was 01/05/1996.

Patients (pts) **:** It consisted of 36 Kostmann syndrome (KS) , 10 cyclic and 7 intermittent neutropenia, 7 glycogenosis Ib, 5 Shwachman syndrome, 3 idiopathic neutropenia and 15 miscellaneous diseases. 60/83 pts received G-CSF (lenograstim, n=27, filgrastim , n=33). The median treatment follow-up since the beginning of G-CSF were 34.2 (range 0.3-68.5); 28.5 ((2.1-64.5), 35.9 (14-57.6), 50.9 (20.9-54.2), 1.9 (0.4-2.9), 19.1 (11.2-34.6), 16.7 (0.3-43.6) months respectively.

Results : Severe side effects were only observed in KS. Two pts experienced leukocytoclastic vasculitis, recoved after G-CSF withdrawal. One patient had previously presented an acute glomerulonephritis with mesangial IgA deposits. Two pts experienced secondary leukemia. In one case the pt had never received G-CSF. KS was diagnosed at age 3 months. The neutropenia remitted spontaneously at 22 years. Ten years later he developed myelodysplasia, that rapidly changed into 6 AML, without cytogenetic anomaly. The second pt received G-CSF during 4.3 years. He developed diabetes insipidus, then myelodysplasia. Cytogenetic examination, performed for the first time, revealed *monosomy* 7 : 47,XY,-7,+21(9) / 46, XY(5). The pt died 10 months later. In 12 pts, cytogenic follow-up did not exhibit anomaly.

Conclusion : Safety- specially in secondary malignancy - is a crucial issue in long term G-CSF therapy. Data of FR-SNC only suggest that KS exhibits a higher risk factor in developing leukemia, regardless pretreatment with G-CSF.

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GROWTH AND GROWTH HORMONE SECRETION IN CHILDREN AFTER TREATMENT FOR ACUTE LEUKEMIA

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This study was conducted to assess the effects of leukemia treatment on growth pattern and growth hormone secretion after cessation of chemotherapy in children with acute leukemia.
Nineteen children with acute lymphoblastic leukemia (ALL) who received UKALL-10 protocol plus cranial irradiation (CI) and three children with acute myelogenous leukemia (AML) who received AML-10 protocol were studied. All of the children were in complete remission for a median of 5±0.5 years.
The mean height standard deviation score (SDS) was decreased significantly during the 6 year period after diagnosis, with the greatest loss being within the first 6 months after diagnosis. After cessation of chemotherapy, it increased slightly but the mean value of final height SDS (-0.59 ± -0.20) was significantly lower than the value at diagnosis (-0.01±0.19) ($p<0.01$). Height velocity SDS was significantly lower (-2.49±0.34) in the first year after diagnosis, compared with the following years. In the ALL group, girls and children with 2400 cGy CI had greater reduction in height SDS than boys and children with 1800 cGy CI, respectively. Growth hormone (GH) secretion in response to insulin induced hypoglycemia and L-dopa stimulation tests was decreased in 6 (29%) of children with ALL, 4 of whom had received 2400 cGy CI. GH secretion was normal in children with AML. None of the children showed sexual maturation abnormality or abnormal gonadotropin secretion.
These findings indicate that CI is at least partly responsible for growth retardation and impaired GH release in children treated for ALL.

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ENDOCRINOLOGIC LATE EFFECTS OF CHEMO-RADIOTHERAPY IN PAEDIATRIC MALIGNANT LYMPHOMA

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Objective: To describe growth and endocrine disorders secondary to chemo-radiotherapy among the long-term survivors of paediatric malignant lymphoma.
Methods: 14 Hodgkin's and 6 non-Hodgkin's lymphoma patients were evaluated. The series comprised 2 females and 18 males, with an age range of 8.87-20.47

years (median: 15.44 years). The follow up varied between 12-148 months (median: 58 months). Patients were evaluated for somatic growth by antropometric measurements (Olcay Neyzi's standards), sexual maturation (Tanner-Marshall's criteria) and bone age (Greulich-Pyle criteria). Thyroid volume, hypothalamic-pituitary-thyroid axis antibodies (anti-M, anti-Tg) were also measured. Hypothalamic-pituitary-gonadal axis was evaluated by assessing basal gonodatropins and gonadal hormones. Gonadotropin peak response to sleep and post-pubertal LH-RH stimulation in retarded sexual maturation was also evaluated. Spermiograms were done in patients whose sexual maturation was over P3 and testicular biopsy was planned in azo-spermic patients.

Results: Heights of all patients were normal. Narrowness of shoulders was observed in one patient receiving "mantle" radiotherapy and obesity in four patients (20 %). Thyroid volume, auto-antibodies, basal levels of the tT3, tT4, fT3, fT4 and TSH were normal, except for one, receiving "mantle" radiotherapy, with elevated basal TSH. Primary hypothyroidism developed in 10 % of 20 patients.

Patients/sexual maturation ratio was 3/P1;3/P2;6/P3;4/P4;4/P5. There was normal sexual maturation in all patients except for one. This azo-spermic 19-year-old patient had elevated FSH levels and impaired Sertoli cell function. Impaired Sertoli cell function was considered in further 7 patients who had elevated FSH levels (40%). Female patients showed normal pubertal development and gonadal functions.

Conclusions: 10% subclinic primary hypothyroidism and 40% impaired Sertoli cell function was present among long term survivors of paediatric malignant lymphomas. Sertoli cell functions were more sensitive to adverse effects of chemo-radiotherapy than ovarian tissue.

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FERTILITY SURVEY IN ADOLESCENTS AND YOUNG ADULT CURED OF CHILDHOOD LEUKEMIA AND LYMPHOMA. A PRELIMINARY REPORT

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In 35 long term survivors of childhood leukemia and lymphoma, 11males and 24 females with medium age 20,5 years (16-29), fertility was investigated 9,5 years (5,5-16,5) after completion of the outlined therapy. Investigation was undertaken on a volunteer basis and included detailed history of sexual maturation and behavior, hormonal survey (T_3, T_4, estradiol, testosterone, sex hormone binding globulin, TRH and LHRH stimulation tests). Additionaly,in females adrenal androgen and US of uter us and ovaries and in males HCG stimulation test and spermogramm were done. From the 11 males examined 2 had complete azoospermia and hypogonadism secondary to testicular irradiation for testicular relapse given prepubertally and one had azoospermia secondary to cyclophosphamide administered at puberty. Remaining males had normal for age sexual maturation and hormonal survey. From the 24 females examined 2 had amenorrhea and severe ovarian damage, one secondary to relapsed Hodgkin's disease and TNI and the other secondary to allogeneic BMT and TBI for relapsed ALL both treated postpubertally 22/24. Remaining females had normal maturation and menses. Four of 34 individuals examined (1 male, 3 females) are now married and have given birth to one healthy child each.

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LATE CARDIAC EFFECTS OF ANTRACYCLINES THERAPY IN CHILDREN WITH MALIGNANCIES: EVALUATION OF REGIONAL DIASTOLIC DISFUNCTION BY PULSED-WAVE DOPPLER MYOCARDIAL IMAGING

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INTRODUCTION

Doppler myocardial imaging (DMI) is a new echocardiographic technique in which it's possible to interrogate the cardiac muscle directly, placing a sample volume in the muscle, with changes in the hardware and in the software of echocardiography.

OBJECTIVE

We evaluated the transmitralic flow by pulsed-wave Doppler (PW-D) compared with the regional diastolic myocardial velocities by pulsed-wave Doppler myocardial imaging (PW-DMI) in four segments (basal and middle interventricular septum, basal and middle inferior wall).

METHODS

To assess the effects of antracyclines (ANT) therapy on left ventricular (LV) diastolic function we employed DMI in 13 patients (pts) off-therapy (mean age 16 yrs, range 8-20) with malignancies, median 108±45 month after last dose of ANT (cumulative dose >360 mg/mq), in absence of cardiac symptoms.

SUMMARY

The pts were divided in two groups, on the basis of E/A ratio calculated with PW-D : first group (G1) with E/A ratio ≤1.33 and second group (G2) with E/A ratio ≥1.34. Seven pts were in the first group and six pts were in the second group. Our data show that in G1 6 pts appear with reduction of regional E/A ratio, almost in one of four investigated segments, for a total of 14/28 (50%) and in G2 2 pts show changes in regional diastolic function, for a total of 3/24 segments (12.5 %).

CONCLUSIONS

The data underline that PW-DMI detects significant abnormalities of global diastolic LV function through evaluating regional diastolic LV function more than PW-D.

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GROWTH HORMONE DEFICIENCY AFTER TREATMENT FOR RHABDOMYOSARCOMA OF THE MAXILLO-FACIAL REGION.

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Growth impairment is a frequent long-term side-effect of cancer treatment in childhood. From July '85 to August '96 12 children (6 boys, 6 girls) were treated in our institution for rhabdomyosarcoma (RMS) of the maxillo-facial (MF) region, age range 1.8 - 11.5 yrs (median 6.3 yrs). Three patients had orbital localisations and the other 9 had parameningeal disease. All were treated with chemotherapy (IVA, Vincaepi, PLADO, IVA/CEV/IVE), 9/12 in combination with radiotherapy (RT) in first line, 2/12 with RT in relapse. Ten are still alive, 7 in 1° complete remission (CR), 2 in 2° CR and 1 in relapse. Of these, 8 are 2 years off treatment, 2 of whom (1 orbital RMS with no RT; 1 RMS of the eyelid in 2°CR with local RT 54 Gy) are now 12 and 6.6 yrs old and are growing well. The other 6 showed a decrease in height velocity and had a full endocrine exploration between 2.4 and 3.2 yrs from end of therapy. Thyroid function was normal. Serum growth hormone (GH) levels remained low during a glucagon and insuline tolerance test (range 2.3-6.9 ng/ml), while cortisol response was normal. All 6 had a spontaneous onset of puberty. Radiation doses ranged from 45 to 56 Gy in daily fractions of 1.5 to 2 Gy. In 4/6 the radiation field encompassed the skull base including the hypothalamic-pituitary (HP) axis in 3 and only the pituitary gland in 1 patient. One child received 24 Gy pancranial irradiation followed by a boost up to 50 Gy on the os petrosum including the HP axis. The 6° patient had a localised RMS and was treated with 54 Gy compromising the HP axis. GH replacement was started in 5/6 children. One girl had already reached final height. Conclusions : out of 12 children treated for MF RMS, 6/10 survivors have proven GH deficiency 2 or more yrs from stopping treatment. In children with non-parameningeal MF RMS, irradiation of the hypothalamic-pituitary axis, should be avoided where possible. All children with MF RMS should be prospectively followed auxiologically and clinically, and if necessary be explored for further endocrine deficiencies.

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LATE SEQUELAE IN CHILDREN TREATED FOR LEUKAEMIA, NHL AND HODGKIN'S DISEASE (HD)

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With successful treatment of childhood malignancies the number of survivors is increasing, but the prolonged survival has been associated with long-term sequelae.

Patients and Methods: Seventy-six survivors (46 boys, 30 girls) were treated between 1971-1991 for leukaemia (27), NHL (11) or HD (38). At diagnosis they were 2-17 years old and had endocrinological (74) and psychological (62) evaluation at the age of 14-34. Pts with leukaemia had chemotherapy (ChT), IT MTX and whole brain radiotherapy (RT), pts with NHL had ChT, IT MTX and RT and/or surgery locally, pts with HD had ChT (32) and/or RT locally (35). For assessment of the endocrine function T3, T4, testosterone and estradiol basal levels and TSH, prolactin, LH, FSH, GH and cortical levels in basal state and after stimulation were measured. The psychological evaluation included Blender Visual Motor Gestalt test and Wechsler Bellevue Intelligence test.

Results: Hypothyreosis was present in 11 pts (all but one had neck RT for HD or NHL), hypogonadism in 29 pts (20 HD, 5 NHL, 4 leukaemia), none had hyposomatotropism or hypocorticism. Psychoorganic syndrome was present in 31 pts (50%), emotional disorder in 47 (76%). Forty-four pts had IQ values between 80 and 110 (normal range), 2 bellow 80 and 16 above 110.

Conclusions: While thyroid dysfunction was found only in lymphoma pts who had (all but one) neck RT, gonadal dysfunction was also present in leukaemia pts. Intellectual and emotional disturbances were fairly equally distributed in the different treatment and age groups. IQ values were bellow normal range only in 2 pts aged 2 and 5 who had RT for leukaemia.

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NEUROPSYCHOLOGIC SEQUELAE OF CHILDHOOD ACUTE LEUKEMIA IN LONG-TERM FOLLOW-UP

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Seventeen children (13 male and 4 female) had been diagnosed as having acute leukemia (16 ALL and 1 ANLL) and have been in follow-up for at least 5 years (5-13 years) were evaluated for neurotoxicity of systemic chemotherapy (ID/ HD MTX) and CNS preventive therapy (CI and IT MTX) which were completed at least 1 year ago. Neuropsychologic testing (WISC-R, WAIS-R), radiological study (MRI) and evoked potentials (EPs) testing (VEP, BAEP) were performed. In the patients with acute leukemia, full-scale IQ and performance IQ were found to be significantly lower compared with the control group made up of 15 age-matched siblings of the patients. MRI studies disclosed CNS abnormalities including leukoencephalopathy, mineralizing microangiopathy and cortical atrophy in 6 out of 17 patients (35 %). Abnormal EPs findings appeared in 5 patients (30 %). Contribution of the age at diagnosis, having meningeal leukemia and receiving IV ID/HD MTX to the neuropsychologic sequelae of the patients was not found to be statistically significant.

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PATTERN OF SECOND MALIGNANCIES IN LONG TERM SURVIVORS FROM CHILDHOOD CANCER. A SINGLE INSTITUTION STUDY

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From 1962 to 1996, 853 children affected with cancer have been treated in our unit, 371 of them were long term survivors from the primary malignancies. Nine of these pts (5 females, 4 males) developed a second tumor (2.4%). Their first cancers were: neuroblastomas (2 cases), ALL (2 cases), HL (2 cases), retinoblastoma (1 pt), hemangiopericytoma (1 pt), hepatoblastoma (1 pt); mean age at onset was 4.6 years (range 3 mos to 12 yrs). Treatments administered for first cancers were: surgery alone in 1 pt; surgery and chemotherapy (CT) in 1 patient; CT and radiotherapy (RT) in 4 patients; surgery, RT, and CT in 3 patients. After a mean time of 9.5 yrs (range 3 to 17 yrs) they developed a second cancer:

pt	1st cancer	2nd cancer
1	Neuroblastoma stage 4s	Promyelocytic leukemia
2	Unilateral retinoblastoma	Hepatocarcinoma
3	ALL	High grade glioma
4	ALL	High grade glioma
5	HL	Papillary thyroidal carcinoma
6	Hepatoblastoma	Papillary thyroidal carcinoma
7	Neuroblastoma	Pheochromocytoma
8	HL	Pelvic rhabdomyosarcoma

The 1st pt developed a stage 4 neuroblastoma 5 years after the first (stage 4s), she received surgery,CT,and RT and long term oral therapy with etoposide.
The 9th patient had a hemangiopericytoma localized in the lower third of the left leg and subsequently another hemangiopericytoma, developed 5 years later, sited at the left shoulder then he developed third hemangiopericytoma, 17 yrs after a second one, sited in the right adrenal gland; he was treated with surgery, CT, and RT and is disease free from 6 yrs.
The child affected with RB (pt 2) had no chromosomial deletion. The distribution of cancers in the family of child who developed neuroblastoma followed by pheochromocytoma (pt 7) seems to suggest a genetic predisposition (MEN type 2). Pts 3 and 4 received cranial prophylactic RT (20 Gys each one), and pt 5 mediastinal local RT. Any significative correlation seems to regard pt 6 who was treated for hepatoblastoma with surgery alone and developed 15 yrs later a papillary thyroidal carcinoma actually in complete remission from 5 yrs.
They all received treatment for their second cancer: surgery alone in 2 pts; surgery and CT in 1 patient; surgery and RT in 1 pt; surgery, RT, and CT in 5 patients. Three pts died of progressive disease, six remained, after the treatment, disease free from 1 to 5 yrs.
Finally we report a case of parotid gland carcinosarcoma occured in a girl, 14 years old, treated with bone marrow transplantation at one year of age, because of major thalassemia. Before BMT she received a conditioning therapy with cyclophosphamide (600 mgx2), myleran (40 mg), then, after BMT, immunosuppression with cyclosporine (40 mg/die) for 45 days. The neoplasm was extremely aggressive and no treatment could shrink the mass allowing surgery; the girl died few months after diagnosis.

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RELEVANCE OF URINARY β_2 MICROGLOBULIN IN THE FOLLOW UP OF IFOSFAMIDE INDUCED NEPHROTOXICITY

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Oxasophosphorines {ifosfamide(I) and cyclophosphamide} are nephrotoxic (N) drugs that cause renal tubular dysfunction. This study is planned to evaluate the value of urinary β2 microglobulin ($U\beta_2M$) in early detection of I induced N.

Patients (pts) and Methods: 23 pediatric malignancies ages between 2-14 treated with I containing protocols were included in the study.$U\beta_2M$ evels were examined at the beginning and at the end of therapy by using Enzyme Linked Fluoresceine Assay. The correlation between the cumulative (C) doses of I and β_2M was investigated.

Results: $U\beta_2M$ measurements before and at the end of therapy were 0.35 mg/L and 4.9 mg/L respectively. 18 (78 %) pts had pathological (> 0.79 mg/L) levels of β_2M at the end of the therapy. Under the C I doses of 18 gm/m^2 5 of 6 pts had normal $U\beta_2M$.The only patient with the pathological level was 2.5 years old. Between the C I doses of 19-36 gm/m^2 all patients were found to have raised levels, of these one had severe (> 6 mg/L) β_2M' uri. Above the C I doses of 36 gm/m^2 all pts had severe β_2M'uri.

Conclusion: C I doses below 18 gm/m^2 can be considered as safe for nephrotoxicity except in very young patients. $U\beta_2M$ is a valuable marker in the follow up of I induced nephrotoxicity.

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EVALUATION OF THYROID FUNCTION IN PATIENTS CURED OF HODGKIN'S DISEASE

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47 patients. who successfully finished treatment for Hodgkin's disease (HD) at least five years ago. were subjected to evaluation of thyroid

function. The duration of remission ranged from 5 to 18,5 years (mean 9,6 years). All patients remained in continuous first remission without significant abnormalities on physical examination and with normal results of laboratory tests.

Thyroid morphology and function were evaluated by physical examination, ultrasonography (USG) and determination of serum levels of thyroid hormones fT_3, fT_4, TSH and TBG.

Control group consisted of 55 age- and sex-matched healthy volunteers. Student t-Test was applied for statistical comparison of the data.

17% of patients had palpable thyroid abnormalities, i. e.: gland enlargement, diminished mobility, increased consistency or nodules. USG revealed heterogeneous echogenicity in 34% of patients and pathological lesions in 21%, respectively.

Patients successfully cured of HD had significantly higher levels of fT_3 (mean=5,4 pg/ml; SD=3,8 pg/ml; p.<0,0005) and fT_4 (mean=1,2 ng/dl; SD=0,3 ng/dl; p.<0,005) and significantly lower serum TBG concentration (mean=17,2 µg/ml; SD=3,8 µg/ml p.<0,005) in comparison to control group.

Conclusions:

1. Patients cured of HD are clinically euthyreoid. Nevertheless, serum levels of fT_3, fT_4 are significantly higher and TBG concentration significantly lower in comparison to healthy control group.
2. Significant group of these patients has palpable or revealed by USG morphological thyroid lesions.
3. USG of thyroid should be repeatedly performed in these patients for early detection of developing secondary thyroid cancer.

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BFM-ORIENTED CHEMOTHERAPY FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IS ASSOCIATED WITH DIMINISHED PUBERTAL SPURT

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Background - Treatment of childhood ALL, with chemotherapy (with or without radiotherapy) may interfere with normal growth of cured patients. Treatment design should consider its safety also in this regard. We studied alteration of the growth velocity with focus on pubertal spurt.

Patients and methods – 50 ALL pts (29 males) aged 4-11 years at diagnosis, treated in the AIEOP ALL 88 study with BFM-oriented intensive therapy, were followed over 4 to 8 years with annual measurements of weight and height; data on ALL type, treatment, parental height were also recorded. Growth pattern was analyzed with the Preece-Baines function, appropriate for evaluation of pathologic growth. Mean growth profiles were also analyzed by the Berkey & Laird linear 2-steps model to correct individual profile estimation.

Results – Main results are summarized in the following table:

	ALL girls	*Normal girls*	*ALL boys*	*Normal boys*
Peak growth velocity (cm/yr)	5.3±0.55	7.47±0.16	7.16±0.54	8.23±0.20
Age at peak velocity (yrs)	10.5±0.24	11.8±0.15	12.0±0.30	14.17±0.15
Age at take-off	133.5±2.8	129.9±1.3	133.5±3.7	138.9±1.0
Height at take-off	133.5±2.8	129.9±1.3	133.5±3.7	138.9±1.0
Adult height	159.9±1.5	163.4±1.1	171.6±2.3	174.6±1.0

Conclusion – Intensive BFM-oriented treatment for childhood ALL is associated with a significant reduction in the pubertal peak growth velocity in both sexes.

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SOME OBSERVATIONS FROM THE FOLLOW UP OF CHILDHOOD MALIGNANCIES AT AN OUT-PATIENT CLINIC

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Late effects of treatment and quality of life have become a major concern following the increased survival of children with cancer in recent years.

Patients and methods: 183 pts (115 male, 68 female), treated 1958-1978 were evaluated at the outpatient clinic of the Institute of Oncology in Ljubljana. They had been 1-9 years old at the time of diagnosis and were evaluated at the ages 19-39 years; 56 had been treated for malignant lymphoma, 33 for leukemia, 33 for brain tumor and 61 for other solid tumors. The examination 1986-1996 included psychological and endocrinological assessment, interviewing about their education, social and religious life.

Results: Hypogonadismus was found in 26 (17.6%) women and 44 (38%)men, but 22 are mothers and 17 are fathers to one or two children Four patients needed special school programs, others have completed or are attending regular schools. The IQ values were below normal range in 4 pts (3 BT and 1 NHL), in 19 they were above and in 160 within the normal range.

Conclusions: In a society where a certain fatalism about cancer is a rather characteristic feature, our patients are adjusting surprisingly well and a majority enjoy normal life, many starting their own families. Our clinic for late effects is not only discovering and helping with emotional and physical shortcomings but also helping these young people, who often are too dependent on overprotective mothers, to become mature adults. The transfer of their follow-up from the pediatric to the adult service should not be unduly delayed.

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Abstract withdrawn.

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SERUM NSE AND CA 125 LEVELS IN THE PEDIATRIC PATIENTS WITH NON-HODGKIN LYMPHOMA

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Elevated serum NSE (neurone specific enolase) levels are common especially in patients with neuroblastoma and high CA 125 levels are seen in patients with ovarian cancer and other gynecological or gastrointestinal malignancies or infections. We describe four children with lymphoma and elevated serum levels of NSE or CA 125 or both.

Patients and Methods: 1992-1996 we have measured the serum levels of NSE and CA 125 at diagnosis in 13 patients with non-Hodgkin lymphoma using radioimmunoassays.

Results: In 31% (4/13) of the pts one or both of the serum concentrations were over the normal limits:

Age	Lymphoma	Location	CA125 kU/l	NSE ug/l
norm. values			(<65)	(0.0-12.0)
3 yr	Burkitt	ileocecalis	126	6
3	Burkitt st IV	liver, BM, CNS	39	144
6	B-like small non-cleaved	abdomen	210	20
14	Large cell anaplastic (Ki-1)	armpit	31	38

All of those values normalized rapidly with therapy and have remained normal. On the other hand, no relapse have seen.

Conclusion: Our results suggest that these nonspecific tumor markers CA 125 and NSE may prove useful in monitoring the activity in some patients with lymphoma especially at follow-up. However, a larger number of patients are needed to see if these findings might have clinical importance.

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MYCOSIS FUNGOIDES IN ADOLESCENT BOY

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Introduction:Mycosis fungoides/MF/is an uncommon indolent lymphoma affecting primarily adults over 50 years of age.It occurs extremely rarely during childhood and adolescence.Here we describe an adolescent boy with tumorous presentation of MF.

Case report:Sixteen years old boy was admitted to our department with two years lasting history of alopecia and patchy skin lessions of the trunk and scalp with subsequent development of the large tumour of the right forearm.Slight unconjugated hyperbilirubinaemia and enlarged thymus were the only remarkable findings by presentation. Pathologist evaluated the tumour specimen as lymphomatoid papulosis.Further course of the disease has made this diagnosis disputable because of steroid resistance and no spontaneous resolution.Partial improvement was achieved with local electron beam therapy.The second biopsy established the diagnosis of MF.The specimen contained monoclonal population of small lymphocytes with T phenotype and large number of Langerhans cells.Mild epidermotropism was present.Patient is currently undergoing PUVA therapy.His prognosis remains poor.

Literature review:There are three documented cases of MF in childhood for the last 20 years.

Conclusion:Low grade lymphomas may occasionaly occur in children.Diagnostic process is difficult and close cooperation between the pathologist paediatrician is necessary.

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IMPACT OF CHEMOTHERAPY (CT) WITH IFOSFAMIDE (IFO) AND CISPLATINUM (CPL) ON EXCRETION OF URINE ENZYMES IN CHILDREN WITH SOLID TUMORS

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Renal function was investigated in 19 children with Wilms tumor(5), rabdomiosarcoma(3), osteogenic(4) and Ewings(7) sarcoma, receiving combination CT including IFO (21 courses, 1800 mg/sq mx5 days) or CPL (23 courses, 100 mg/sq m/day). Creatinine and urea concentration of blood serum and excretion of urine enzymes N-acetyl-β-D-glucosaminidase (NAG), alanine aminopeptidase (AAP) and γ-glutamiltranspherase (γ-GT) were determined before, during and after CT and compared to age-matched controls. Before treatment urine enzymes activity was the same as in control group and cut off for: γ-GT- 9.5, AAP - 4.4 and NAG - 0.6 U/mmol creat. The significant elevation of urinary enzymes excretion was observed in both groups of patients during CT compare to initial values and controls ($p< 0.01$-0.04), but the extent of enzymuria elevation in children treated with IFO was significantly higher ($p<0.01$) than in CPL treated group. 19.4 time elevation of NAG was observed after IFO treatment, while after CPL it was 5.9 times. Excretion of AAP and γ-GT was less remarkable than NAG in IFO treated group. In CPL teated group AAP and γ-GT elevation was prominent with significanse close to NAG elevation. In contrast to altered excretion of urinary enzymes, serum creatinine and urea concentration remained within the normal range in majority of cases. Clinical presentation of renal insufiency as retention of fluid, proteinuria, microhaematuria and elevation of creatitin level observed in two patients on IFO was associated with a very high level of NAG elevation (9.5-43.2 U/mmol creat) never seen before CT. The results obtained suggest that urinary ensymes are sensitive indicators of early renal impairment.

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THE IMPORTANCE OF SERUM MURAMIDASE ASSESSMENT IN HODGKIN'S DISEASE

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It is known for a long time that assessment of serum muramidase (SM) can be of significance in many diseases. assessment technique is simple and from laboratory apparatus requires only spectrophotometer. We have assessed the level of SM in 38 patients (pts) with Hodgkin's disease. SM were performed before initial therapy, and every two months during therapy.

In stage I of the disease, mean SM values were 9.8 mg/l; in stage II mean values were 14 mg/l; in stage III 26 mg/l and in stage IV Hodgkin's disease mean SM values were 30 mg/l. In remission, SM mean value reached normal level (4±1.2 mg/l). In one pts with resistant form of disease SM values were during therapy slightly lower than initial. In two pts SM levels risen one month before clinically determined relapse of the disease. Assessment of SM levels during Hodgkin's disease, from our point of view, is useful because values of SM tend to behave as disease activity biological marker.

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PRIMARY LYMPHOMAS OF RARE LOCALIZATION IN CHILDREN

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Presented material was obtained from the Pathology Department connected with oncologic unit specialized in treatment of solid tumours in

children. Thus the collection contains only such cases, which were clinically unsuspected toward lymphomas or systematic diseases. Although we have diagnosed some cases of primary lymphomas of rare localization. There were 11 primary malignant lymphocytic lesions without the nodular or broad medullar involvement. The age range was 4-20 yrs, boys domination 10:1, averange age 11 yrs. The most numerous cases were osseal: 3x femural, 2x tibial,1 maxillar, vertebal, pelvical. We have also diagnosed two primary lymphomas in kidneys, and one testicular. With one exception there were B line malignancies in the oldest cases no immunocytochemistry was performed.
- The most common among rare localizations of primary lymphomas seems the osseal one with the dominant incidence in boys.
We have also observed two cases of uteral and ovarian localization, but we have not receive evidently sure clinical data to treat them as primary cases.

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THYMIC CYSTS AFTER CHEMOTHERAPY AND RADIATION IN A PATIENT WITH HODGKIN'S DISEASE

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Mediastinal masses play a key role in Hodgkin's disease. They may be present at diagnosis, they may remain after therapy or appear after adequate therapy. We report a patient with Hodgkin's disease who was found to have a new mediastinal widening two months after completion of chemotherapy and radiation to the mediastinum. Hodgkin's disease Stage IIA, nodular sclerosis, with cervical and mediastinal involvement was diagnosed in a 15 year old male. He received 2 courses of ADR, VCR, VP16 and PRD followed by radiation (30 Gy) to involved fields. Cervical nodes had disappeared completely while a few paratracheal nodes were still present after radiation. Two months after radiation with the patient in excellent health, a chest X ray showed a large right paracardial mass. Echocardiography revealed a cystic structure, noncontiguous to the myocardium. This was confirmed by computed tomography. 70 ml of clear fluid were aspirated from the largest cyst which was 5-6 cm in diameter. No evidence of Hodgkin cells was found and further intervention was not considered necessary. The mass disappeared completely within the next 2 months. The patient has remained in remission for now 3 years.

Cystic mediastinal masses arising after therapy have been described in both Hodgkin's disease and NHL. They represent tissue reactions of the thymus to either chemotherapy or radiation. Because of their benign nature invasive investigation or further therapy are not required.

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OUTCOME OF AN INFANT WITH BLADDER RHABDOMYOSARCOMA PRESENTING DIFFERENTIATED RHABDOMYOBLASTS

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A 7-month old girl was admitted in October 1994 to our Clinic with a lower abdominal large mass. Abdominal ultrasound and MRI showed a 10 cm pelvic mass pressing the bladder, displacing intestinal loops to the right and pushing the stomach upwords. Skeletal and chest X-ray, as well as urinary HVA/VMA, alpha phetoprotein and betaHCG were normal. Bone marrow aspiration was normal too.
Surgery was performed a first time, and an esophitic tumor (11x9x9) was removed along with the bladder dome, to which the tumor was attached. Histopathological findings revealed a vesical embrional RMS with one iliac lymphnode involved. Due to microscopic residual disease a second partial cistectomy was performed with radical intent, but unfortunately margins of resection were infiltrated; this time a pathological analysis showed the presence of sparse differentiated rhabdomyoblasts
So chemotherapy (CT) was started according to the AIEOP RMS 88 protocol for clinical group II B (IRS staging). After two 7-weeks courses of Ifosfamide, Vincristine, Actinomycin-D (IVA), without radiation therapy, to avoid unfortunate sequelae in such a small child, it was decided that a more intensive CT should be implemented. After the first cycle of Carboplatin, Epirubicin, Vincristine (CEV), according to SIOP MMT Stage IV protocol, surgery was performed again with subtotal excission of the bladder, making a gastric patch and leaving the trigone untouched. Also this time a histopathological examination revealed an entire bladder wall infiltration from several rhabdomyoblasts, the main part of which had advanced differentiated features; that was also confirmed by an immunohistochemical investigation using antibodies against skeletal muscle specific actin and desmin.The same CT was continued with 2 cycles of CEV alternated by 2 cycles of Ifosfamide+Vincristine. A control MRI didn' t show any evidence of disease and CT was stopped in November 1995. Another MRI, three months later showed a 0,6 cm esofitic mass of the bladder. A cistoscopy with multiple biopsies was performed and showed the presence of advanced differentiated rhabdomyoblasts; gastric mucosa was normal. The child was followed, every three months, with ultrasonography; 15 months after the end of therapy, the child is in good clinical condition, with functioning bladder.
The persistence of differentiated rhabdomyoblasts at the end of therapy, rarely documented in literature, has created a dilemma whether or not it should be considered as evidence of active tumor. Considering the positive experience reported by Ortega et al. (Abs Med Pediatr Oncol 1996; 27 : 222) and by D'Amore et al. (Mod Pathol 7: 69, 1994) in patients with differentiated rhabdomyoblasts, our strategy in this child was a strict clinical and radiological follow-up, without other treatment.

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HEPATOSPLENIC γδ T-CELL MALIGNANT LYMPHOMA: REPORT OF A CASE IN CHILDHOOD.

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Peripheral T-cell lymphomas are clinical and morphologically heterogeneous tumours, rare in childhood. They express surface T-cell receptors of the α-β type in the vast majority of cases. Recently, few peripheral T-cell lymphomas bearing γδ T-cell receptors have been reported. Hepatosplenic γδ peripheral T-cell lymphomas are rare and aggressive tumours with predominant hepato-splenic and bone marrow involvment. We report a case of a 2-year-old male with γδ T lymphoma. He was first seen for persistent fever unsuccessfully treated with azitromicine. When patient was admitted, clinical findings included conjunctivitis with blepharedema, mild hepatosplenomegaly, bilateral inguinal micropolyadenia and antalgic gait. X-ray examination, TC scan and increased uptake of Tc^{99m} identificated osteomyelitis of left tibia. Surgical biopsy suggested a diagnosis of chronic osteomyelitis. Patient was unsuccessfully treated with ceftriaxone and netilmicin. After two months he developed iperpirexia, cough, wandering papuloerithematous rash without pruritus associated with hepatosplenomegaly and inguinal lymphadenopathies. Over the following days physical examination showed a nodule (2 cm in diameter) on the left plantar region. Skin biopsy was performed. Histological examination and immunohistochemical analysis led to the diagnosis of T-cell malignant lymphoma. Frozen sections were processed for molecular analysis. Detection of γδ receptor suggested the diagnosis of "Hepatosplenic γδ T-cell lymphoma". In this child mediastinum was involved but no neoplastic cells were detected on CSF and bone marrow. Initial treatment with intensive drug combination including prednisone, vincristine, cyclophosphamide, daunomycin and methotrexate was started and partial remission was achieved. During the consolidation phase the patient experienced a relapse involving liver, spleen and cervical nodes. A complete remission was achieved after treatment with VP16. After one month a skin relapse occurred. The patient underwent a unrelated cord blood transplant, DRB1 and DQ mismatched. The conditioning regimen was cyclosphosphamide 60 mg/Kg/d for 2 days and TBI (six fraction of 200 cGy over 3 days). GVHD prophylaxis consisted of cyclosporin A, steroids associated with ALG. The engraftment was successful for neutrophils on day +14 and for platelets on day +53. He experienced a bacterial sepsis and developed a grade II aGVHD. At present, the patient is alive in complete remission, at 4 months from transplant and 9 months from diagnosis.

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ADVANTAGES OF EXOFOLIATIVE CYTOLOGIC ANALYSIS AND FNA BIOPSY IN THE DIAGNOSIS OF MALIGNANT LYMPHOMA IN CHILDREN

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From 1979 to 1996 there were 89 cases of malignant lymphoma diagnosed at the Children `s Hospital Zagreb by cytological analysis. In this work the results of exofoliative or FNA cytologic diagnosis in 24 children are shown, because in this group it was the only possible method due to the severity of the clinical picture and the poor general condition of the children. In 19 children the results of exofoliative cytologic diagnosis were as follows; in nine children diagnosis was made by analysis of ascites: five were HL, and four were NHL. In ten children analysis of fluid pleural drain shown: eight NHL and two HL. In one child the diagnosis was made by analysis of the cerebrospinal fluid: it was NHL. In four children the diagnosis was made by FNA biopsy. In three children the diagnosis was made by analysis of puncture lymphonode of the neck: in two children were HL, and in one child NHL. In one child the diagnosis was made by analysis of FNA bipsy node of the testicles: it was NHL.
In the analysis of pleural drain and ascites immunologic phenotyping confirmed the cytological analysis, and in some patients latter pathohistological diagnosis was confirmed by cytological diagnosis. The importance of exofoliative or FNA cytodiagnosis is stressed since sometimes it is the only possible method and also offers the possibility of immunoligic phenotyping and cytogenetic analysis.

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THYROGLOSSAL DUCT CARCINOMA IN A PEDIATRIC PATIENT. A CASE REPORT.

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Thyroglossal duct cysts are the most common anomaly during development of the thyroid gland. They are twice as frequent as branchial arch abnormalities and, in children, are second only to enlarged cervical lymph nodes as the cause of neck masses. Thyroglossal duct carcinoma is extremally rare expecially in childhood.

A boy 8 years and 4 months old was admitted to the Hospital S.Camillo in Rome, for a neck mass noted by the parents four months earlier. On physical examination, a mass, 2 cm in diameter, was evident in the anterior midline of the neck. It was easily displaced by palpation and was neither tender, nor painful. An ultrasound examination showed a solid mass with normal thyroid echostructure. Laboatory studies were normal. A thyroglossal duct cyst was then suspected and surgery was performed using the Sistrunk procedure. It entails resection of the entire cyst and tract, the dissection going back to the foramen caecum at the base of the tongue and included removal of the midportion of the hyoid bone.
At surgery the mass (2 cm in diameter) was solid, parenchymatous, dark-red in colour, and looked like a thyroid tissue. The post operative period was uncomplicated and the child was discharged 2 days later.
Histology revealed a thyroid papillary carcinoma excised with a thyroglossal duct cyst.The tumour extended to the surrounding tissue in mutiple scattered foci. The child was then re-admitted for further investigations. Chest X-ray films were normal, ultrasonography showed a thyroid gland normal in volume and echostructure and no nodular lesion were reported. No lymph node enlargement was noted in the cervical region. Thyroid scintiscan showed a normal radioiodine uptake, but diminished in the left lobe. A CT scan of the chest was normal. No further treatment was administered except for a long term thyroidsuppressive treatment initiated 4 months after surgery. Work up showed: carcinoembryonic antigens (CEA) < 3 (n.v.<3 ng/ml), thyroglobulin <7 ng/ml, (n.v.<60 ng/ml) and calcitonin: 12 pg/ml, (n.v.3-25 mg/ml). Monthly follow-ups (physical examination nd ultrasound) continue: 14 months after surgery the child remains free of disease.
Cancers developed in the thyroglossal remnants are of two principal types: squamous cell carinoma arising from metaplastic columnar cells, and thyroid carcinoma arising from thyroembryonic rests.
Treatment is controversial. Complete asportation of the cyst and the associaed thyroglossal duct is indispensible; recurrence is certain after incomplete resection. The Sistrunk procedure dating from 1928, is the method of choice

A review of the literature (115 cases) showed that management varied widely. Some employed only the Sistrunk procedure, other were more radical adding lymph node dissections, thyroidectomy or both. These and other variations have been advocated for both adults and children. The Sistrunk operation is sufficient for non metastatic disease in our opinion. Thyroidectomy should be reccomended only when there is objective evidence of a mass or a nodule in the thyroid gland. Radical or modified radical neck dissection is indicated only in the presence of biopsy proven positive lymph nodes. Because of prolonged natural history of papillary carcinoma (20 yrs or more), long term follow-up is needed.

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HODGKIN'S DISEASE OCCURRING IN A CHILD AFTER LIVER TRANSPLANT

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Background Post-transplant lymphoproliferative disorders (PT-LPDs) are usually related to immunosuppressive therapy and EBV infection. They range from polyclonal proliferations - regressing with immunosuppression withdrawal - to aggressive B-cell lymphomas. Hodgkin's disease (HD) is not included among these conditions, rarely occurring in kidney transplant recipients. Only one example of LPD after liver transplantation, morphologically resembling HD has been reported in the literature.
Methods In 1987, a 4-yr-old boy affected by post-Kasai biliary atresia underwent liver transplantation. Following surgery, the administration of Cyclosporine A and prednisone was started. In May 1994, the patient developed left cervical lymphadenopathy. A lymph node biopsy was performed and studied on morphologic, phenotypic, and molecular grounds.
Results The biopsy showed typical mixed cellularity (MC) HD. Neoplastic cells expressed CD15 and CD30, being negative for CD45, CD20, CD3, CD43, and CD79a. Furthermore, they carried the EBV-related products LMP-1 and EBER1/2. The patient received 3 cycles of ABVD, followed by radiotherapy (2,000 cGy_s). Tolerance, toxicity and response to therapy were similar to those of all other children treated for HD. Immunosuppression was reduced during therapy, but not discontinued, and finally increased because of incipient rejection. At present, the patient is alive and in complete remission.
Conclusions Our case represents the first proven example of HD following liver transplantation. The positivity of neoplastic cells for LMP-1 and EBER1/2 indicates a possible role of immunosuppression in the development of the tumour, whose pathobiology however seems to be quite distinct from typical EBV-driven PT-LPDs: in fact, the integration of the virus is observed in about 90% of MCHD cases, independently of a previous history of organ transplantation. Clinical course in the present case suggests that patients with PTHD should be treated by standard chemo/radiotherapy. It remains however open to question whether it can be convenient to reduce immunosuppression and to monitor the course of the disease before starting chemotherapy, as usually done in conventional PT-LPDs.

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CLINICAL, HISTOLOGICAL, IMMUNOHISTOCHEMICAL AND MOLECULAR CHARACTERISTICS IN A MALIGNANT PARAGANGLIOMA

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Paragangliomas (PGL) are uncommon mostly benign and slow growing neoplasms that arise from neural crest cells. We report a non-functioning, retroperitoneal PGL without histopathological evidence of malignancy but with local invasion and bone metastases with special attention to histological and immunohistochemical data.
Case: A 16 yr old girl was presented with a large (>700 ml) mass in the upper right abdominal quadrant. Catecholamine level and other tumor associated activity parameters were not elevated. Resection of the tumor showed a nearly complete encapsulated mass with multiple necrotic and bleeding areals. The tissue was consisted of moderate polymorph elongated epitheloid cells arranged in nests in a vascular stroma. The cells showed no elevated mitotic activity or atypic mitoses. Immunohistochemistry revealed strong reactivity for chromogranine A, a myelin basic protein, and S-100 protein, the marker of the PGL-typical sustentacular cells, for NSE, synaptophysin, vimentin, whereas no reaction to the cytoskeletal markers cytoceratine and desmine was found. In RT-PCR, telomerase, the enzyme that elongates telomeric DNA, was not expressed. A postoperative MIBG-szintigraphy revealed a significant MIBG-uptake of a bone lesion in the vertebra. A CT-directed biopsy with the identical histology of the PGL was the cause to intend radiochemotherapy and the resection of the lesion. Long term follow up including MIBG-szintigraphy is required.
Discussion: Bone metastases are common and may be the only clinical sign for malignancy in PGL. Surgery is the treatment of choice. A few reported cases including chemotherapy, radio- and MIBG-therapy are inconclusive so far. Long term follow up is essential in this slow growing tumor. Cellular atypia and

mitotic rate is reported not to be correlated with the clinical behaviour of PGL. Actually, telomerase-negativity may be a hint to benign growth as the enzyme may be essential for unlimited cell proliferation and malignancy. Correlation of immunohistochemistry and malignancy are partly consistent with reported data: thus, in the malignant PGL the neurogenous should be more pronounced than cytoskeletal differential signs. In summary, immunohistochemical data are not unequivocal and may be without significance on individual patient with PGL.

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AUTOIMMUNE HEMOLYTIC ANEMIA AS PRESENTING DISORDER OF HODGKIN'S DISEASE

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Immune dysregulation in Hodgkin's disease (HD) is commonly defined as immunodeficiency state, but autoimmune disorders have also been described. We report a patient who presented with autoimmune hemolytic anemia (AHA) and HD as underlying disease.

Case report: A 15-year-old male presented with a 10-day history of jaundice and pallor. Spleen was palpable at 5 cm under the costal margin. Warm-type antibody AHA was confirmed by laboratory findings: severe normochromic and normocytic anemia, increased reticulocyte count and indirect bilirubin level, intense positive direct and indirect Coombs test. Abdominal sonography revealed multinodular splenomegaly and enlarged retroperitoneal nodes. Laparotomy with splenectomy and limph node biopsy was performed at once. HD with lymphocytic depletion was the histologic finding in the spleen but lymph nodes were reactive. Beside surgery, therapy was directed against HD, type LD, st I B and consisted of 8 alternative courses of COPP and ABVD. Hemolytic anemia was limited to a single episode and its evidences disappeared one week after splenectomy, although Coombs test was positive for another 5 months. Patient is in continuous complete remission 12 months after diagnosis.

Conclusion: AHA revealed abdominal onset of underlying HD and permited early diagnosis. Therapy directed against HD was convenient to AHA.

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TREATMENT RESULT AND PROGNOSTIC FACTORS IN NONMETASTATIC EWING'S SARCOMA - 10 YEARS SINGLE INSTITUTION EXPERIENCE

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OBJECTIVE: Our study was aimed to evaluate results of treatment and analysis of prognostic factors in patients with nonmetastatic bone ES treated with combined modality approach.

PATIENTS AND METHODS: From 1985 to 1994 we treated 51 patients (pts.) with nonmetastatic Ewing's sarcoma, median age 13,5 (range 2 yrs - 25 yrs) The majority of them were in high risk group (33 pts. had large tumors with volume >100 ml. The greatest number of patients had central localization of the tumor - 27 pts. All pts. received systematic chemotherapy, mostly VAIA or EVAIA protocol. After primary chemotherapy in 28 pts. was performed conservative surgery followed by radiotherapy and 23 pts. had definitive radiotherapy. Conventional fractionation was given in 39 pts. and hyperfractionated accelerated schedule in 12 pts.

RESULTS: During the follow-up period from 1 year to 9 year (Me=3yrs) overall survival rate was 45% and disease-free survival rate was 35%. 25 pts. failed to combined therapy: 16 developed distant metastases, 5 local recurrence and 4 both types of relapse.

Analysis of prognostic factors showed that tumor volume was a significant factor influencing prognosis. 3-years overall survival rate was 67% for pts. with small tumors (volume less than 100 ml) compared to 33% for pts. with large tumors (volume greater than 100 ml). In pts. who had surgery for local control, the histologic response to chemotherapy had strong influence on survival: 3-years overall survival rate was 80% for pts. with less than 10% viable tumor (good responders) compared to 40% overall survival rate for pts. with more than 10% viable tumor (poor responders). Analyses of survival rates separately for pts. with different primary tumor site (proximal extremity lesions, distal extremity lesions and central primary site) showed no significant difference.

CONCLUSION: Tumor load and responsiveness to chemotherapy are two major factors influencing prognosis in pts. with primary Ewing's sarcoma of bone.

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HEMOLYTIC ANEMIA AND FATAL CAPILLARY-LEAK SYNDROME IN A PATIENT WITH MEDULLOBLASTOMA WHO RECEIVED CARBO-PLATINUM-BASED CHEMOTHERAPY (SIOP/ PNET III REGIMEN)

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Capillary leak syndrome is a rare, severe disorder with a high mortality rate. It consists of the loss of fluid and proteins from the intravascular to the extravascular compartment with subsequent hypovolemic shock. Mechanisms of capillary leak syndrome are poorly understood. We describe a 14-year old girl with PNET (medulloblastoma) who was on carboplatinum (CDBCA) -containing chemotherapy (SIOP/PNET III Regimen). This patient had mild Coombs-negative anemia following the first two doses of therapy. After the third doses of chemotherapy, she was hospitalized because of febril neutropenia. She was still on G-CSF (5 ug/kg/day) and no focal infection was evident. Imipenem + amicasin was promptly started, and CSF was discontinued. In the third day of hospitalization, clinical picture of capillary leak syndrome developed with hypotension, peripheral generalized edema and weigth gain followed by prerenal azotemia. The renal function detoriated and the diffuse edema worsened without a rise in blood pressure, in spite of an intensive fluid replacement therapy with crystalloids, blood, plasma, albumin transfusions, dopamine and steroids. On the fifth day of therapy, massive pigmenturia (probably reflecting myoglobulinuria) developed. She did not respond to therapy and pulmonary edema developed. She died of cardio-pulmonary arrest on the ninth day of hospitalization. During the full course of hospitalization, the patient was fully conscious, and she did not show the classical picture of severe neutropenic septicemia. Also, the clinical course was different from septicemia-related multiple organ failure and capillary leak syndrome. The lung vasculature had been spared until the last day of clinical course. The etiological factor must be different. CDBCA-induced hemolytic anemia was reported. To our knowledge this is the first report of hemolytic anemia and capillary leak syndrome in the same patient receiving CDCBA-based chemotherapy.

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NON HODGKIN'S LYMPHOMA ASSOCIATED WITH JEJUNAL ADENOCARCINOMA IN A YOUNG GIRL WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Occurrence of multiple malignancies in children is a rare condition especially when particular genetic or chromosomal abnormalities are absent. Second malignant tumors, mainly sarcomas or leukemias, developing several years after cancer treatment have been observed. They are attributed to radiation therapy or use of some cytotoxic drugs. We report here the case of a 7 years old girl with simultaneous diagnosis of two malignant tumors whose association has not been described so far.

The patient was 4 years old when she developed clinical and biological signs suggestive of systemic lupus erythematosus. While she was receiving corticosteroids, severe vomiting led to identification of a filling defect in the jejunum on barium contrast. Symptoms resolved spontaneously, but few months later, because of compressive multiple anterior mediastinal lymph nodes, she became dyspneic. Biopsy revealed T cell lymphoblastic non Hodgkin's lymphoma. Vomiting and hematemesis recurred soon after initiation of chemotherapy with unchanged radiologic pattern of the jejunum. The patient underwent laparotomy and complete excision of a 3 cm size jejunal tumor was performed. Histology revealed intramucosal adenocarcinoma. Almost one year later, the patient is alive in complete remission.

The association of these two malignant tumors in a young patient in the absence of family history of polyposis or cancer rises the issue of predisposing factors to cancer. Whether preexisting systemic lupus erythematosus could play a role is to be considered.

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BURKITT'S LYMPHOMA OF CHILDHOOD: 15 YEARS OF EXPERIENCE AT EGE UNIVERSITY

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Between 1980 and 1995, 30 patients at Burkitt's lymphoma were diagnosed in the Pediatric Oncology Department of the Medical School of Ege University. The median age of patients was 5 years with a sex (M/F) ratio of 2/1. Ziegler system was used in staging. The majority of the patients (80%) were in advanced stages (C and D) at initial diagnosis. Abdomen was the most common primary site of tumor involvement (73.3%) which was followed by jaw (10%) and peripheral lymp node (10%). The majority of the patients (66.7%) were received treatment according to the modified Ziegler regimen. 7 patients died during the observation period or in the early stage of their therapy, and 6 patients in the late period. Metabolic complications were the major causes of death. The relaps occured in 7 patients. Four of them had CNS relapse. The three years relaps-free survival rate for all patients was 60%. There was no significant difference in survival rates between the early and advanced stages ($p>0.05$).

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The Immunophenotypic Classification of Childhood Non Hodgkin Lymphoma

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This study was performed in 25 patients with histologicallyconfirmed non-Hodgkin lymphoma at the University of Çukurova, Department of Pediatric Hematology-Oncology the years between 1989 and 1996. All cases were immunophenotyped from paraffin sections. A positive reaction for L26 was interpreted as indicating a B cell immunophenotype and UCHL-1 was interpreted as indicating a T cell immunophenotype. 68% of cases were B cell, 20% were T cell, 12% were non-B non-T cell type. The study revealed that disease free survival was significantly longer in the B cell patients (p 0.05).

When the correlation with the histological subtype and the immunophenotype were taken into consideration, small non-cleaved cell lymphoma of cases were B cell (p 0.0001). When the correlation with the histological subtype and the site of origin were taken into consideration, small non-cleaved cell lymphoma of cases were in the abdomen(p 0.0001). There was a negative correlation between the age and the prognosis (p 0.0001).

Finally, immunophenotype is an important prognostic factor in childhood NHL. When the treatment strategy is choosen, immunophenotype must be a criter with stage and histologycal subtype.

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LIMB SALVAGE OR AMPUTATION IN BONE TUMOUR- OUR RESULTS

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In the period from 1990.-1995. at the age from 6-18 yrs there were 20 children with diagnosis osteosarcoma and 23 children with diagnosis Ewing sarcoma treated at the Children's Hospital Zagreb- Center for solid tumours. In our report we presented result of treatment depending on operation method-limb salvage or amputation. 17 children with osteosarcoma had tumour on lower limb. Among children with Ewing sarcoma the same localisation was found in 11 cases. Preoperative chemotherapy was performed with 15 children with osteosarcoma and all of the others with Ewing sarcoma. Limb salvage and implantation endoprothesis- model Kotz was done in 8 children with osteosarcoma and 2 children with Ewing sarcoma. Among all the others the partial resection without implantation of endoprothesis was done. 2 children with limb salvage and 3 children with amputation in osteosarcoma group had lethal outcome. In Ewing sarcoma group 3 children with limb salvage and 2 children with amputation had lethal outcome.

According to the results we would like stress the seriousness of the decision for operation which has to be founded after detailed analysis of bone scyntigraphy and computer tomography scans which explains the eventual infiltration of soft tissue. In postoperative treatment we would like to stress necessity for intensification of chemotherapy with we can achieve successful result of bone tumour treatment.

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MANAGEMENT OF CHILDREN WITH ABDOMINAL NON HODGKIN LYMPHOMA IN MOROCCO

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Morocco is a developping country which gives priority to prevention. However, since1980, cancers in children and particularly Non Hodgkin Lymphoma are being treated in Moroccan units of pediatric oncology. We report 154 abdominal NHL (ANHL) diagnosed between 1990 and 1994, investigated and treated in the Pediatric Hemato-Oncology Unit of Rabat. These 154 ANHL represented 64 % of all sites NHL (241). The sex ratio was 2.7 / 1, the mean age being 5 years and 7 months (2 - 15 y). The diagnosis was done by laparotomy (10), peripherical biopsy (6) and cytology of tumor or liquid (138). The histology showed a high grade of malignancy, mostly of the Burkitt type (120); the immunophenotypage was not done. According to Murphy staging, 5 patients (pts) were in stage II, 142 in stage III and 7 in stage IV. Ten pts received no treatment (8 died before and 2 families refused).144 pts has been treated according to the French Protocols LMB 84 and 89. Our results were as follows: 31 pts died before achieving Complete Remission (CR), 25 of them died during the first 15 days, mainly from metabolic complications, 4 resisted to treatment, and106 pts reached CR (73,6%). Out of this last group, 18 relapsed (9 abdomen, 5 NM, 4 testis, 2 BM) with 4 prolonged second CR, and 6 died in first CR (CR1). The follow-up of the 82 patients remaining in CR1 was less than 1year in 31 cases, between 1 and 3 years in 27 cases and between 4 and 6 years in 26 cases. The overall survival rate of all144 treated patients was only 63%, because of the early deaths and the lack of prolonged follow up. The Overall Survival Rate of the 106 patients who have acheived CR was 90 %. In conclusion, management of children with ANHL in developping countries is to be encouraged despite technical and organizational issues which are specific to each country.

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TREATMENT OF B NON-HODGKIN'S LYMPHOMA ACCORDING TO LMB89 PROTOCOL IN CASABLANCA

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From September 1990 to December 1995, 67 cases B non-Hodgkin's lymphoma have been treated according to French LMB 89 protocol. Therapy is stratified according to 3 prognostic groups with escalating doses and duration of chemotherapy. Age ranged from 2 to 17 years with male/female ratio of 2,9. The main site of the tumor is abdominal (53/67). The other involved sites are tonsils (8 cases), maxillary (3 cases), both abdominal and maxillary (2 cases) and orbital (1 case). According to Murphy classification, 8 patients are stage II, 48 patients are stage III and 11 patients are stage IV. 5 patients, early lost to follow-up are not evaluable. Of the 62 remaining patients, 1 is bad responder to prephase chemotherapy and 7 others have not achieved complete remission at the end of the protocol. 10 patients (16%) have died during induction therapy, 5 of hematologic toxicity and the other of nutritional and metabolic complications. 44 patients (70%) have achieved complete remission. 5 of these patients have relapsed, 2 have died during consolidation therapy of hematologic toxicity and 5 were lost to follow up in complete remission while the others (51%) are still in first complete remission with a follow-up ranging from 12 to 76 months. Overall survival and disease free suvival after 36 months follow-up are 59% and 57% respectively.

These results are below what is expected in patients treated according to this protocol in France. This is due to high rate of initial toxic deaths.

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WILMS TUMOR: TIME BETWEEN SURGERY AND THE BEGINNING OF THERAPY AS A PROGNOSIS FACTOR.

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Survival rate in Wilms tumor (WT) is influenced by age, stage, and the presence of anaplasia. Delay in starting treatment is not supposed to occur, and has not been thoroughly evaluated.

We report our 16-year experience with 30 pts to determine whether delay in beginning treatment after surgery influenced prognosis.

For this purpose patients were divided into two groups: Group A: Surgery and chemotherapy (CTX) done in our institution (22 patients). Mean time of delay was 5 days (1-14). Group B: Surgery elsewhere and referred for CTX. Mean time between surgery and CTX was 23 days (15-120).

Patients of group A were treated according to NWTS protocols (6 received preoperative CTX because of tumor size). Patients of group B were overtreated following the same protocols.

Both groups were comparable for age, surgical staging and, histology type. One patient in group A presented with relapse during treatment while five patients in group B presented with relapse during or after treatment or progression of disease that lead to death in three of them, in spite of treatment with second line protocols.

We conclude that delay in starting treatment adversely affects prognosis. Surgery for WT should be done in specialized centers where complete treatment can be offered to the patient.

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PERCEPTION OF ILLNESS THROUGH PSYCHOLOGICAL ASSISTANCE IN CHILDREN WITH CANCER

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It's well known that children with cancer have the perception of their illness, and demonstrate it through the simbolic language. If you consider and interpretate the fantasies, feelings, anxieties and experiences expressed in the child play, it's possible to have the child psychoanalitic comprehension (Klein, 1955). Using the play technique, it's possible to detect the uncounscious fantasy of both illness and cure even in the first session (Aberastury, 1982). The Psychology Service offers assistance to all children with cancer and their parents. We follow the comprehension of the child psychoanalitc psychotherapy theory allied to the technical comprehension of the focal psychotherapy (Fiorini, 1989). In this study, we intend to show that perception of illness is expressed through psychological sessions. Six cases of children with cancer aged between 4 and 12 years old were chosen at random. They were in different phases of the medical treatment: diagnosis (2), relapse (2) and paliative care (2). Using in this six taped cases the same methodology of the theory and technique of assistance it was possible to notice that children with cancer have the perception of their illness, possibility of cure and the death threat. These results were found even in patients with different ages and medical treatment phases. We realize that with these interventions it was possible to help children better comprehend their feelings and so, reduce their anxiety. In so far as children with cancer have conscious of their illness, the staff could consider it in the management of the cases.

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AN EDUCATIONAL INTERVENTION TARGETING TOBACCO USE IN PEDIATRIC CANCER PATIENTS

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We examined the effects of an educational smoking intervention on knowledge of tobacco-related health risks, perceived vulnerability to tobacco-related health risks, and intentions to use tobacco among preadolescent and adolescent cancer survivors. Patients were one to two years from completion of cancer treatment and between 10-18 years of age. Of 11 patients enrolled on the study to date, five survivors were previously treated for Hodgkin's Disease, four for lymphoma and two for solid tumors. The mean age of the cohort was 14.2 years (SD=2.3). The proportion of males (n=5) and females (n=6) was approximately equal and the majority of patients were white (10/11). The mean time from diagnosis was 27.8 months (SD=9.0). Patients were randomized to either a Standard Care Control (SCC) group or a Smoking Education Intervention (SEI) group. Patients were stratifed on the basis of age, race, and smoking status prior to randomization. Patients assigned to the SCC group were advised about tobacco-related health risks, and encouraged to abstain from or stop using tobacco. Patients in the SEI group received more intensive intervention that targeted the patient's increased vulnerability to tobacco-related health problems relative to their healthy peers. The intervention consisted of: 1) an educational video, 2) smoking literature and self-quit materials for current tobacco users, 3) goal setting and contracting, and 4) follow-up telephone contacts. Results indicated that 4/11 (36%) were current or past tobacco users. For patients in the SEI group, knowledge scores and perceived vulnerability scores increased from pre-to post-intervention by 15.0% and 9.5%, respectively. Intention scores decreased from pre- to post-intervention by 2.0%. Collectively, the findings demonstrate that patient perceptions of vulnerability to tobacco-related health risks, tobacco-related knowledge, and intentions to smoke can be modifed with appropriate educational intervention. We will continue to accrue patients (for an anticipated total of n=25) and plan to report 6 and 12 month follow-up data (n=10).

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CHILDHOOD CANCER DOES NOT LEAD TO INCREASED SOMATIC CONCERNS: A Controlled study of Young Women Surviving Leukemia

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Objective **This population based case-control study examined whether experience of cancer in childhood leaves a hypersensitivity to various somatic symptoms. Further, are self-reported somatic symptons explained by medical late-effects or a worry of recurrence of the cancer.**
Subjects **Of the total of 44 female survivors of leukemia, 42 were studied. The survivors were compared with 69 age-matched healthy controls.**
Methods **Self reported somatic symptoms by a questionnaire, medical late-effects evaluated by pediatric haematologist, and worry about recurrence on the basis of interview.**
Results **Unexpectedly, young survivors of leukemia reported fewer somatic symptoms than healthy age-matched comparison subjects (P<0.001). Late physical sequelae were uncommon except in the survivors of allogeneic bone marrow transplantation. Of the survivors, 52% were afraid of recurrence of the illness. The presence of physical or visible impairment and worry of recurrence were unrelated to frequency of somatic symptoms.**
Conclusions **The results suggest that experience of cancer and its treatment does not lead to increased somatic concerns or hypochondriacal tendencies.**

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THE PSYCHOSOCIAL ADAPTATION AND DEPRESSION IN THE FAMILIES OF THE CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Acute Lymphoblastic leukemia (ALL) is the most frequent childhood malignancy. Leukemia effecting the child both physically and psychosocially also concern the family dynamics.The child's disease catapults the family is also reflected to the child causing a vicious circle. It is critical to bear in mind that "The patient is the family not only the child." In our study we examined the psychosocial adaptation and the incidence of depression among the families of 75 children with leukemia (25 in1st diagnosis,25 in relapse, 25 in terminal phase) and compared to the families of children with Acute Rheumatic Fever using family interview forms, Family assesment Device and Beck Depression Scales.The results were compared with x , student's t- test and ANOVA computer programme. The result of the study showed that the parents of the leukemia patients are more affected in the first relapse than the first diagnosis in respect to family relations, affection and depression levels.In the terminal phase, parents were the most affected ones compared to the first relapse group. Also the mothers are found to be more depressed than the fathers in all group . The controlgroup are not depressed at all (n: 20).
In conclusion, the parents of the children with leukemia are more effected for family relations and depression levels compared with the parents of children with acute rheumatic fever and they need psychological help.

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PSYCHOLOGICAL SUPPORT DURING THE TREATMENT OF ADOLESCENT PATIENTS WITH TUMORS

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Ten adolescents with cancer followed for at least two years from diagnosis were included in this study. All patients spent long periods in hospital. Six of them were fully informed of the diagnosis while the remaining four were only partially aware of their disease. All patients were referred to the psychological team because of difficult relation with the pediatric oncologist. We tested the hypothesis that adolescents in therapy use defense mechanisms typical of their age group that is not comparable to normal defense mechanisms previously identified (Soccorsi, Terapia familiare, 1984, 16:47). To analyze individual situations, meetings were held with the adolescent and his family during the hospitalization or the visit in day hospital. A certain similarity in the behavior patterns of eight of the ten patients was immediately evident - the refusal to identify themselves with other patients even those of the same age group (rejection of communal meeting places, i.e.); ambivalent attitudes towards the parents alternating between dependence, aggression and rejection; mistrust of the therapy staff with the exception of one member, chosen as a privileged interlocutor; abnormally violent side effect reactions to drugs (vomiting, nausea, etc.), with consequent intolerance of treatment. For the remaining two adolescent the almost total absence of the family provoked different reactions which swung between adult and child like behavior. The analysis of this behavior compared to the behavior patterns of the healthy adolescent (Baldascini, Terapia familiare, 1994, 47:25) lead us to read these patterns as a defense mechanism against "intersystem paralysis". The lack of normal relationship systems (family, peers, adults, with whom the adolescent usually interacts) prevents him/her from experiencing separation, a fundamental element in a healthy evolution process. He/she thus finds himself back in a dependence situation from which he had been breaking away. The idea consequently arose of using the presence of individuals not immediately identifiable with the hospital staff and more easily associated with relationships established before the illness. Thus, an "outsiders" operation began with school teachers and voluntary groups of students aged 18 - 22 years working in the hospitals. The main objective is to re-establish - even if only partially - the relationship systems which are necessary to establish and consolidate identify, despite the illness.

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ANALYSIS OF PERSONALITY TRAITS IN

CHILDREN TREATED FOR CANCER.

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The aim of the study was to investigate changes of personality traits in children which were diagnosed as having leukemia or other forms of cancer and were treated with chemotherapy.
Patients and methods. In total 106 children entered the study. Two groups of children were selected: in group A - 51 children treated between 1983 - 1991 were included and group B consisted of 55 children treated since 1992 - 1996. The later group of children was placed in addition on the programme of the medical and psychological support. The following psychological tests were used: Cattell`s questionnaires (CPQ, HSPQ), Manifest Anxiety Scale and Spielberger`s inventories (STAI, STAIC).
Results. Analysis of the results obtained indicates that children which underwent cancer therapy show some characteristic changes which depends on the age at diagnosis as well as a period of treatment and facilities of the ward where chemotherapy is performed. Children treated without full required psychological and medical support in comparison with children which received full programme of psychological support exhibit worse general mental ability ($p<.05$), emotional instability ($p<.05$), submissiveness ($p<.005$), desurgency ($p<.05$) and introversion ($p<.05$). Younger children from both group showed tendency to sizothymia, introversion, anxiety, guilt proneness, internal restraintion and high emotional tention.
Conclusions.

1. Children treated without possibility of full required psychological and medical support exhibit more difficulties with personality adjustment than the other group.
2. Younger children (8-12 yrs) in general show more personality difficulties comparing to the group of children which were older during therapy (12-18 yrs).
3. During the course of therapy changes in personality traits were observed in individual children.

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HOUSE-DRAWINGS BY CHILDREN AFFECTED WITH CANCER

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Drawing is a priviledged way of expression in infancy. By drawing a child tries to reproduce the images of the reality he acquainted from birth; to own the reality, but also to control the anguish he feels when this reality changes.
Psychoanalysis considers children drawings like the dreams, a preferred way to the comprehension of thechild unconscious. The analysis of drawings allows us to better understand child's inner world, the conflicts, the difensive mechanisms and the expectations. M. K. De Kuitica & Coll. (1989) wrote that the analysis of child's drawing implies not only the awareness on the activity of "drawing" but also on formal elements which make the drawing: visual and kinetic, allowing the evaluation of general meanings.
Nevertheless "Fè d'Ostiani" (1987) underlines the importance of the use of space and colors, the quality of tract, particulars, distance between objects, strange or wrong elements, child's comments and feelings that drawing arises in the operator.
The house is one of the first non-animated object drawn by children; A.Aberastury states that house drawing represents symbolically the child's body scheme.
In our Pediatric Oncology Service, we analysed 20 house-drawings of accepted children and compared them, with house-drawings by health children.
Many differences emerged between the two groups and in the pediatric oncology one we have identified a few common elements, here underlined:
- lack of the floor (as: lack of the filter between instintual and conscious world)
- presence of monumental, ovoid-shaped, shut doors (as difficulty to feel coping)
- scene and house usually placed on the left or the central side of the sheet. (as to reveal in drawings the events of their inner wold related to the story of family dynamics).

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Abstract withdrawn.

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TO BE OR NOT TO BE INFORMED ABOUT THE DIAGNOSIS OF CANCER?
AN EXPERIENCE OF THE PAEDIATRIC CLINIC OF FLORENCE

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Consensus about the utility of providing full information to the young patient with cancer has been reached in people of Anglo-Saxon culture. However, not necessarily the same principles will apply in other ethnical contexts. In fact, in Latin countries the traditional approach to severe illnesses in children has been one of "silence". In an effort to apply the principles of "honest and accurate" information about diagnosis, prognosis and terapy, and hoping to reduce the anxiety related to a diagnosis of cancer, we have informed, directly or through the mediation of parents, pediatric patients managed at the Pediatric Hematology-Oncology Service of the University of Florence since 1988.
Patients and methods: A total of 16 patients partecipated in the study, 8 males and 8 females, age 8 to 22 years. also 17 parents of 12 different children were involved. Diagnosis were the following: ALL 9, solid tumors 5, solid tumor + ALL 2. Terapy: 9 vere in terapy, 7 off-therapy. The duration of tratment varied from 5 to 50 months (median 23 months). Parents: 8 parents in pairs; 6 mathers and 2 fathers. Schooling: 33% had finished elementary school. 50% secondary and 12% hight school. Socio-economical status: 50% low, 25% medium, 25% hight. For both children and parents a structured and standardised interview was performed according to Van Velduisen and Lost. To measure anxiety and depression Qestionair Scale for the Developmental age and "Children's Depression Inventory"(CDI) developed by Maria Kovacs were performed. The communication style is represented in a sumscore (range 0-10), that is the additional sum of different aspects of the comunication style. Results: None of the patients use the term "cancer" but 2/3 of the parents used the term "Leukemia or Tumor", all children were told that their disease is long-lasting, 50% that is serious. 25% of the parents discussed the possibility of relapse or death. All parents explained treatment procedures and side effects. 75% during the first few days after diagnosis. Only 25% had difficulties discussing the disease with their child. No difference of awareness within the age range studied was noted. Questions relating to their disease were asked by 2/3 of the patients, generally at an early stage of disease. 1/3 of the children did not ask anything either because they did not want to know anyting , or bacause they tried to protect their parents by not talking about it. More than 1/3 of the children tried to conceal their distress about the disease in an attempt to protect the parents and to protect themselves from dealing with the parents distress. With regard to the intensity of anxiety and depression had a lower average score than normal. only one patient was on the edge of a patological depression. The correlation between the comunication style and the intensity of anxiety and depression were not significant, but they show that an open style of comunication leads to less negative emotion on the part of the children, less anxiety in school and towards the environment, and less depression. Conclusion: Our findings show that children who are informed about there disease are less anxious and depressed than children informed later or not at all, they show better adaptation to the environment and improved school attendance. A open comunication style is important to avoid severe depression and comunication difficulties within the family (the law of double protection).

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ALL-ROUND-CARE IN CHILDHOOD ONCOLOGY: EARLY INTERVENTION AND SUPPORT OF EXISTING FAMILIAL AND PSYCHOSOCIAL STRUCTURES VERSUS REHABILITATION FOLLOWING TREATMENT

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Children with malignant disease are often treated in major centers far away from their home. The period of intensive therapy at the beginning, and later, for example due to a relapse, disrupts the habits of life, the relations within the families and the psychosocial bindings. If the disease eventually is overcome, sometimes it is very difficult to reverse social isolation and to enter normal life again.
The Department of Hematology and Oncology in Gummersbach was founded in 1994, sponsored by a very active self-help group of affected parents, to provide maximum level treatment near the domicile of the patients. This intention met with medical considerations favouring an "open patient guidance": Even in aplasia, sepsis might be treated easier and more successful, if the